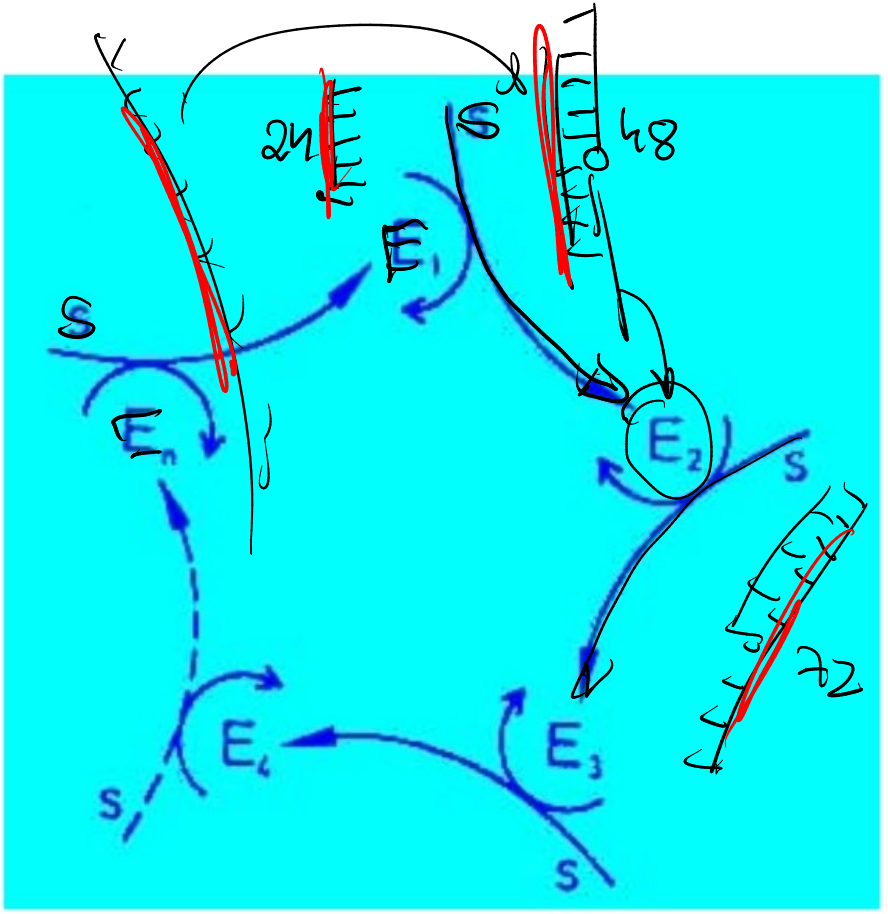
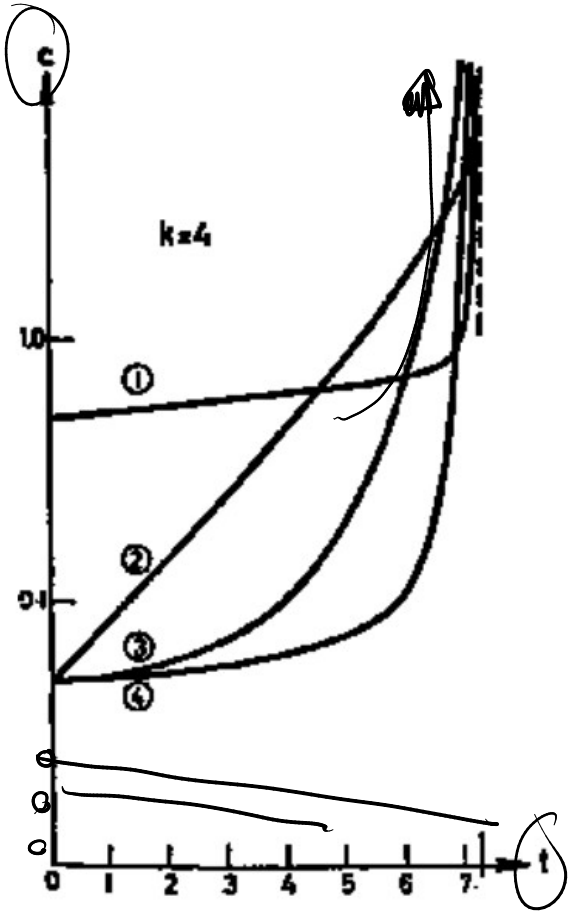
Sequence Hypercycles
by Competitive Ligation

Hypercycles

Manfred Eigen and Peter Schuster 1977

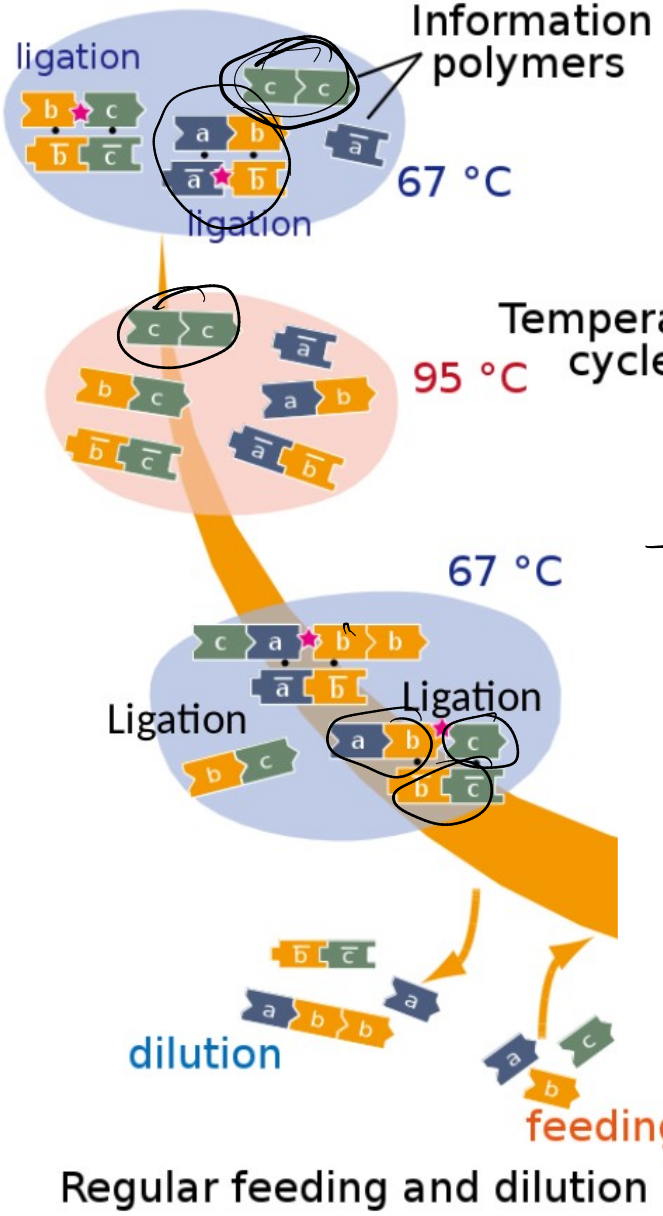




Dream: Hyperexponential Replication

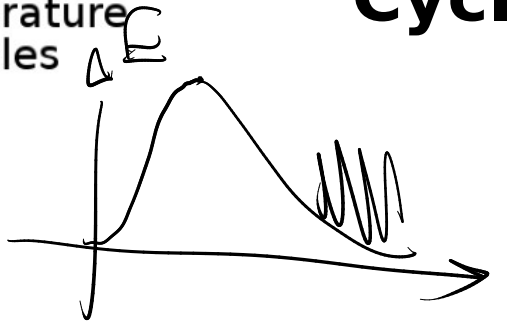
Only theory and not robust against 'viruses'

Long Term Replication by Ligation



>1000 Temperature Cycles

Shoichi Toyabe

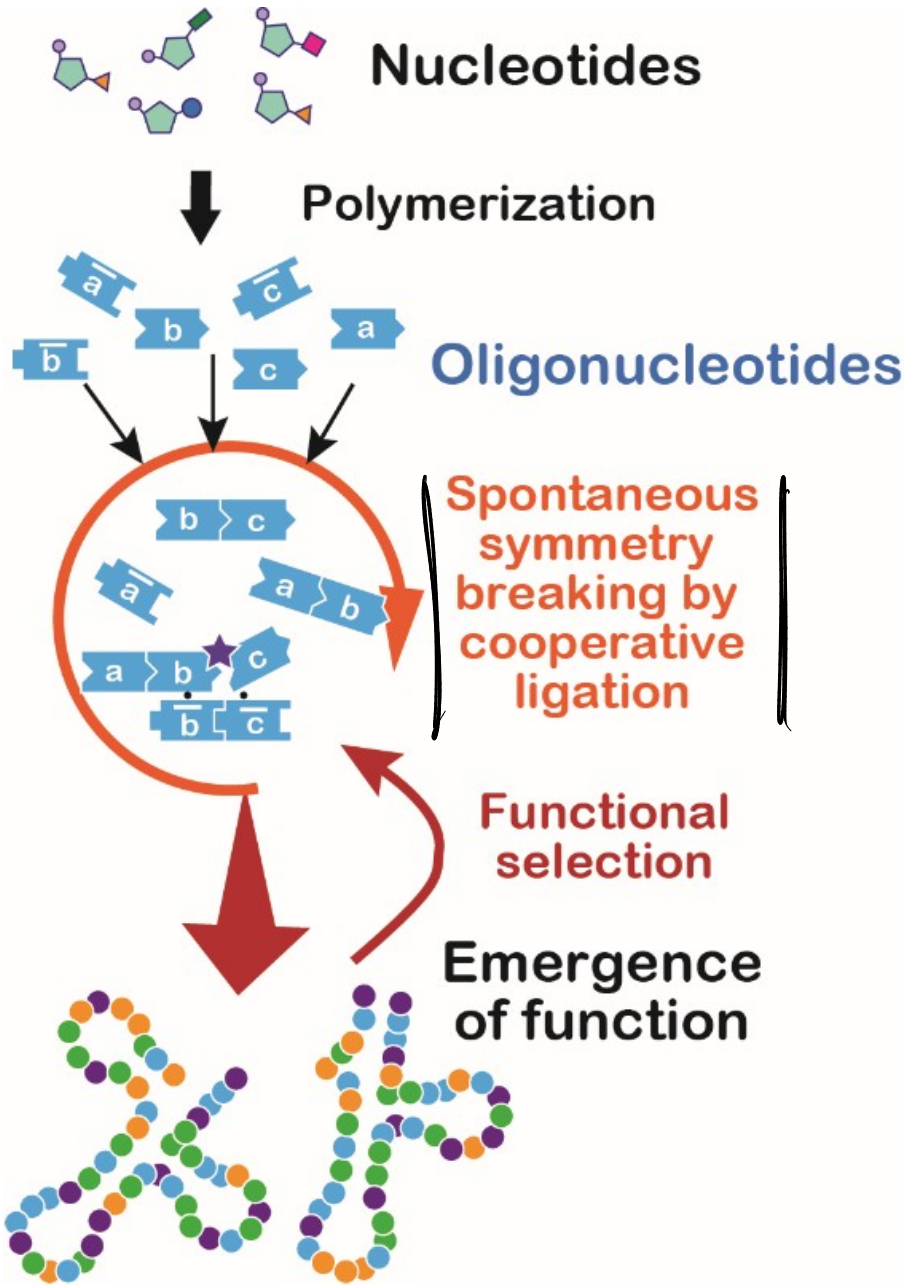


Using Taq DNA Ligase

Ligation of 20mers
A=a,$\bar{a}$ B=b,$\bar{b}$ C=c,$\bar{c}$

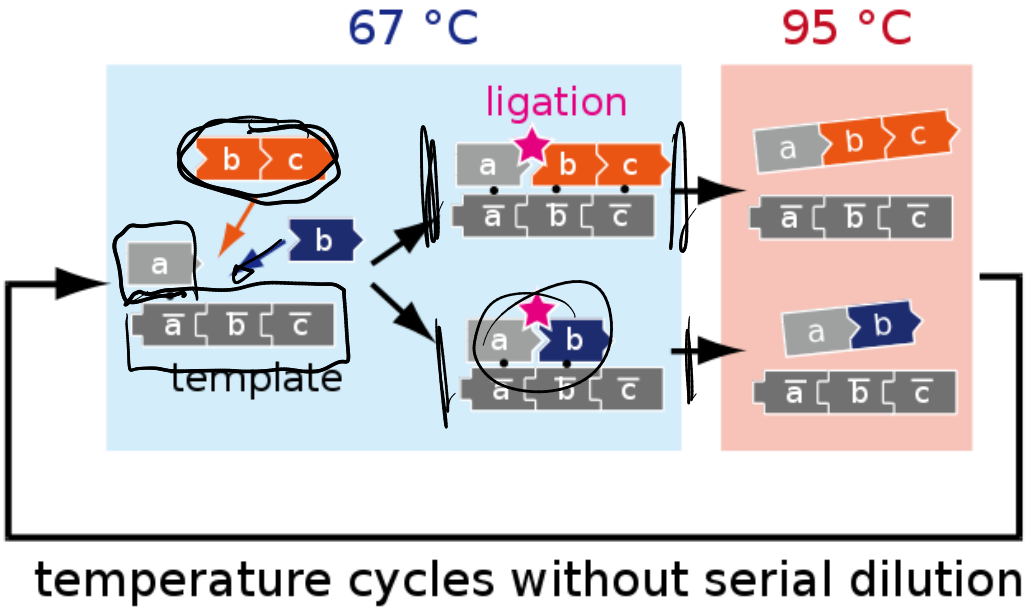
Detection of sequences AB,AC... using quantitative cold PCR

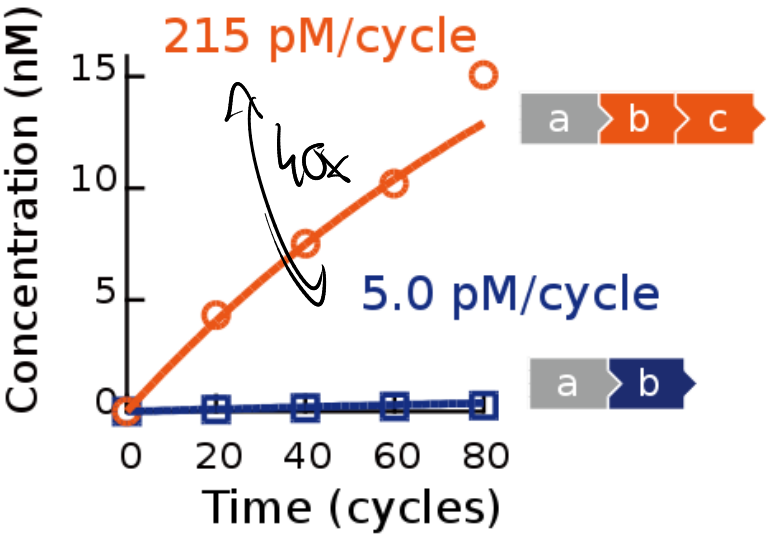
Long Term Replication by Ligation



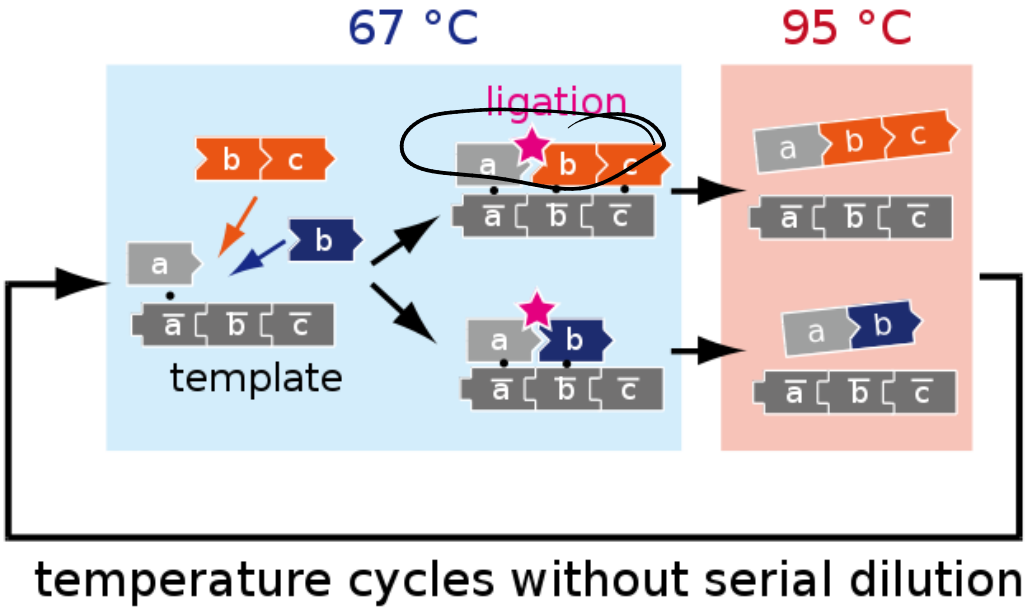
Shoichi Toyabe

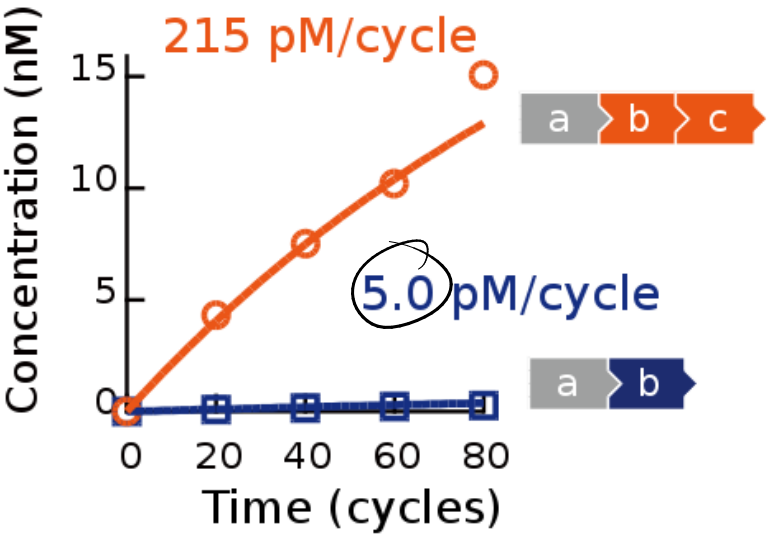
Competitive Ligation (linear mode)

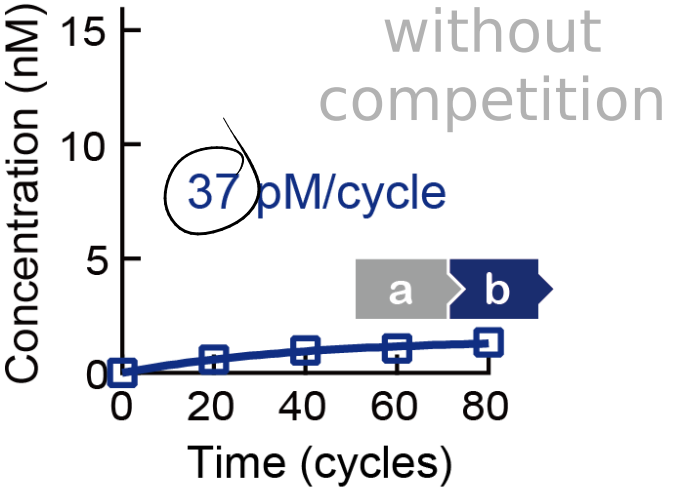




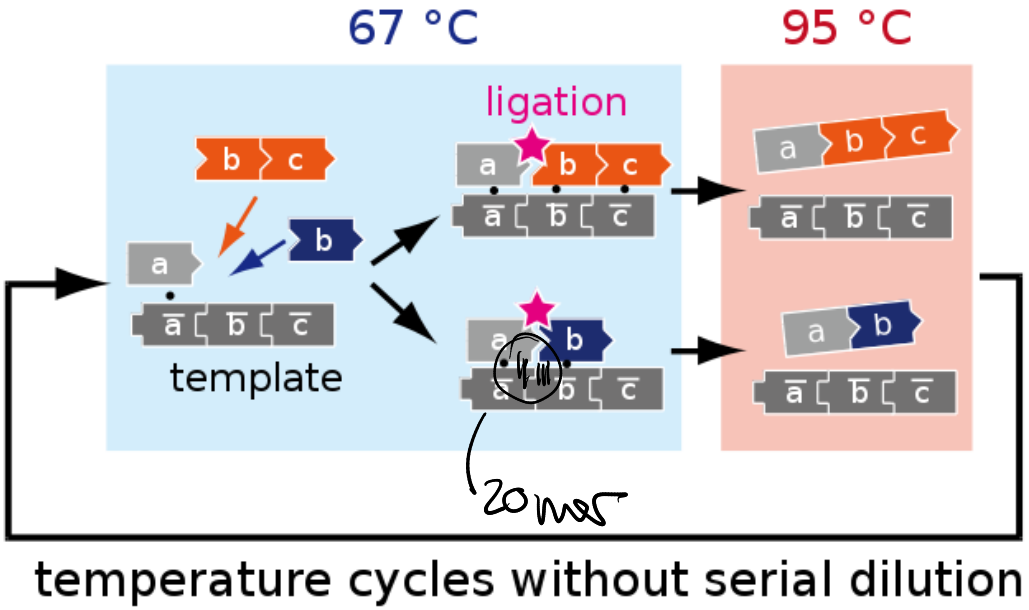
Competitive Ligation (linear mode)

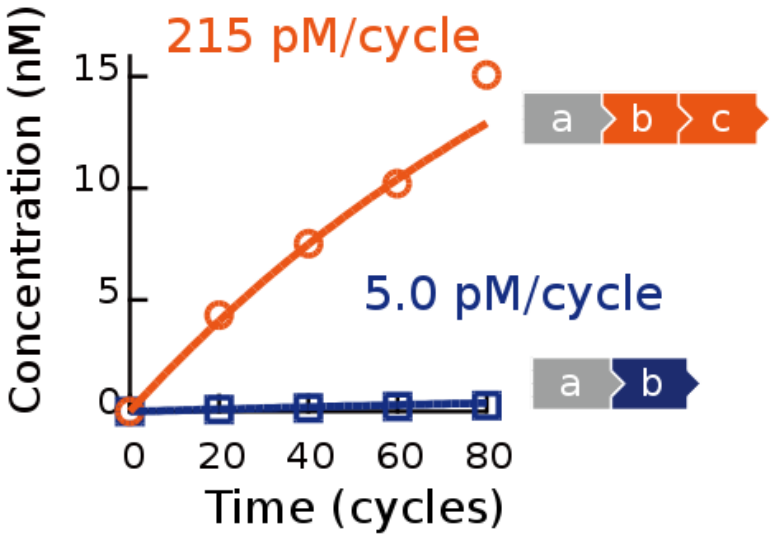




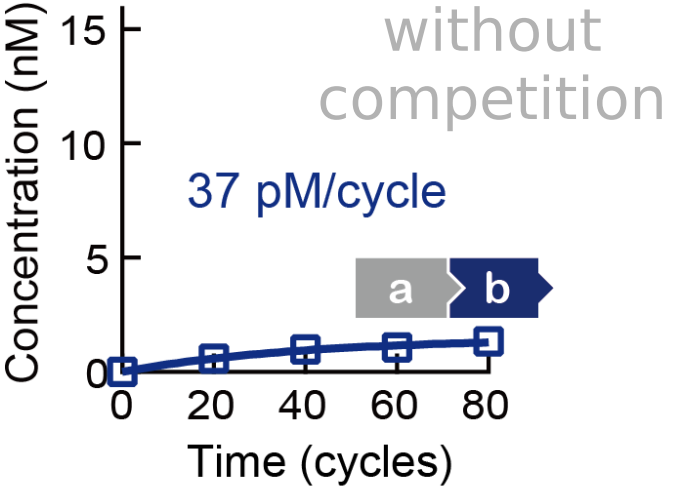


Competitive Ligation (linear mode)





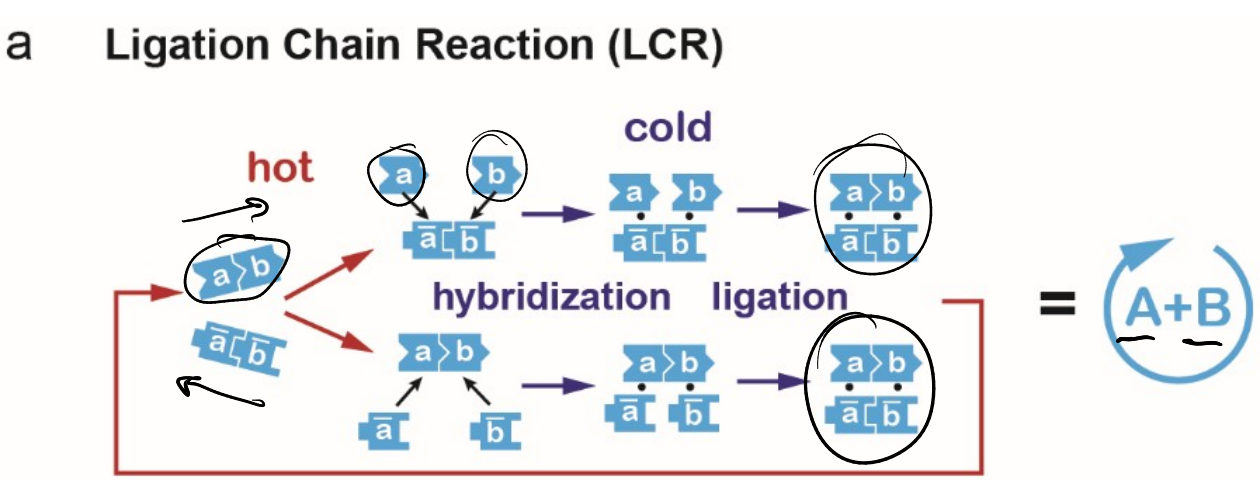
Ligation is sensitive to sequences beyond the ligation site:

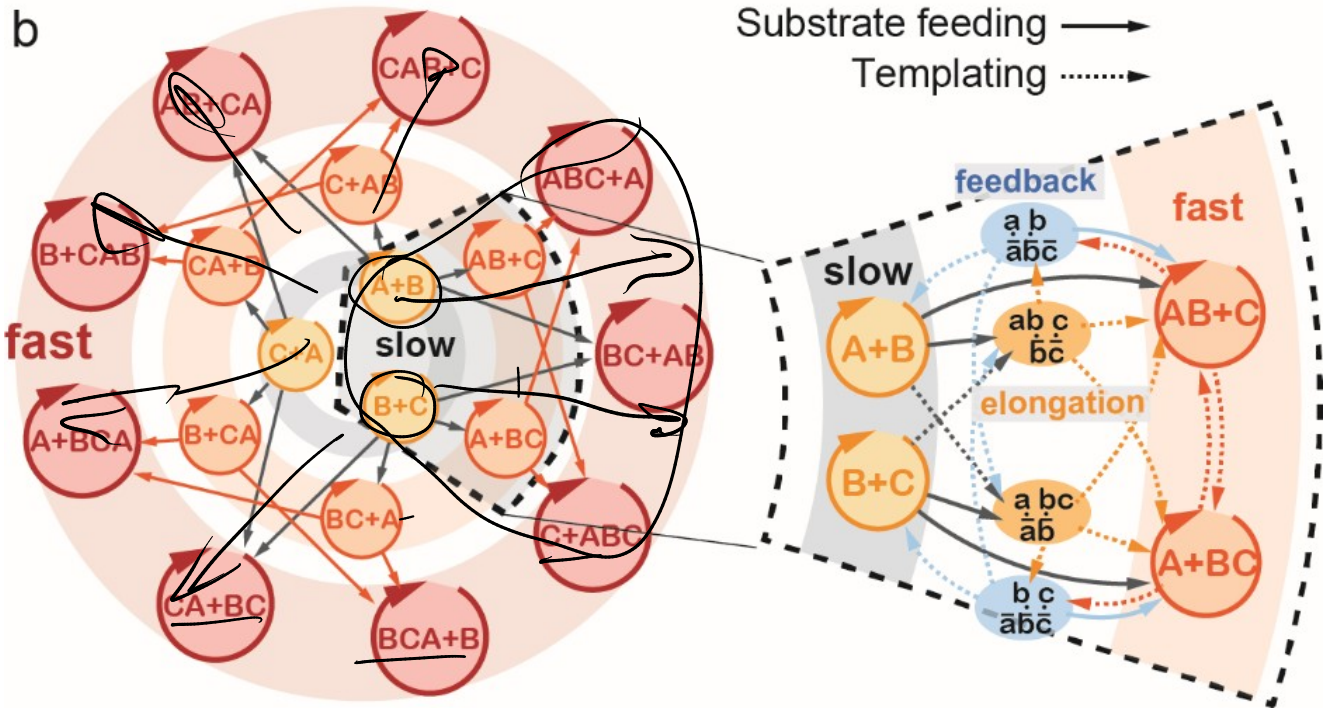


=> Generation of long range sequence correlations ?

Cooperative Replication by Competitive Ligation?

Cooperative Replication by Competitive Ligation?

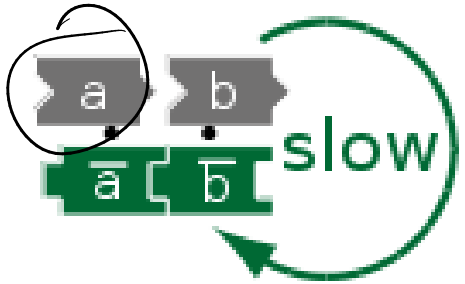




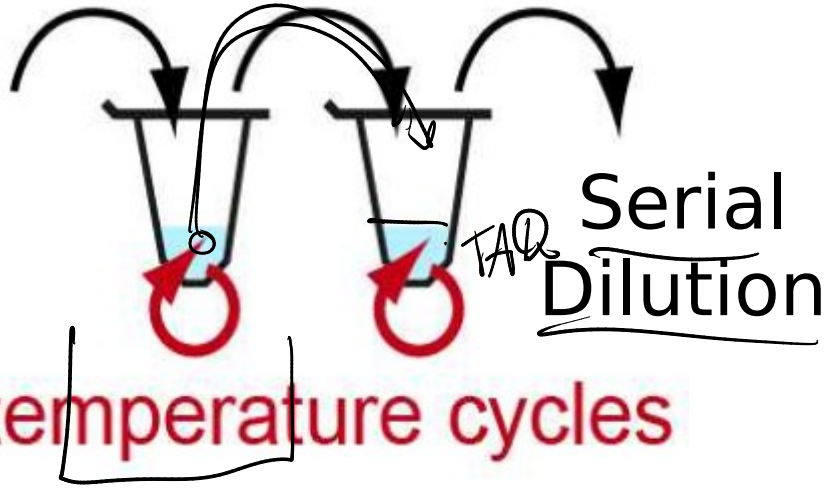
Cooperative Replication by Competitive Ligation?

Exp. Replication by feeding a,b,$\bar{a}$,$\bar{b}$

AB



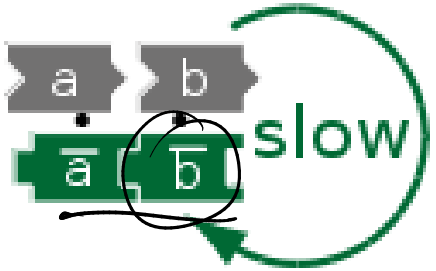
Survival against simulated degradation



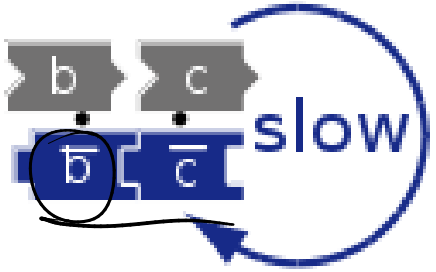
Cooperative Replication by Competitive Ligation?

Exp. Replication by feeding a,b,$\overline{a}$,$\overline{b}$

AB



BC

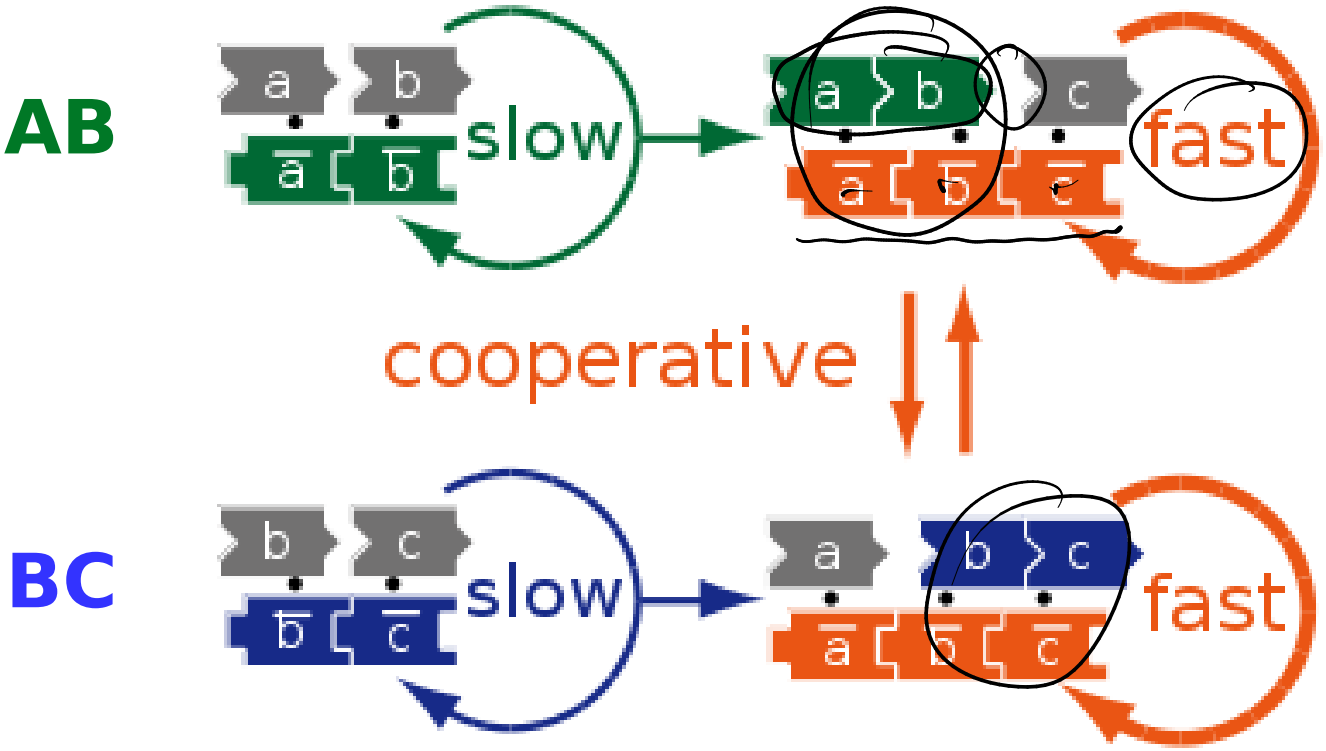


Exp. Replication by feeding b,c,$\overline{b}$,$\overline{c}$

Cooperative Replication by Competitive Ligation?

Exp. Replication by feeding a,b,$\bar{a}$,$\bar{b}$

Cooperative Sequence

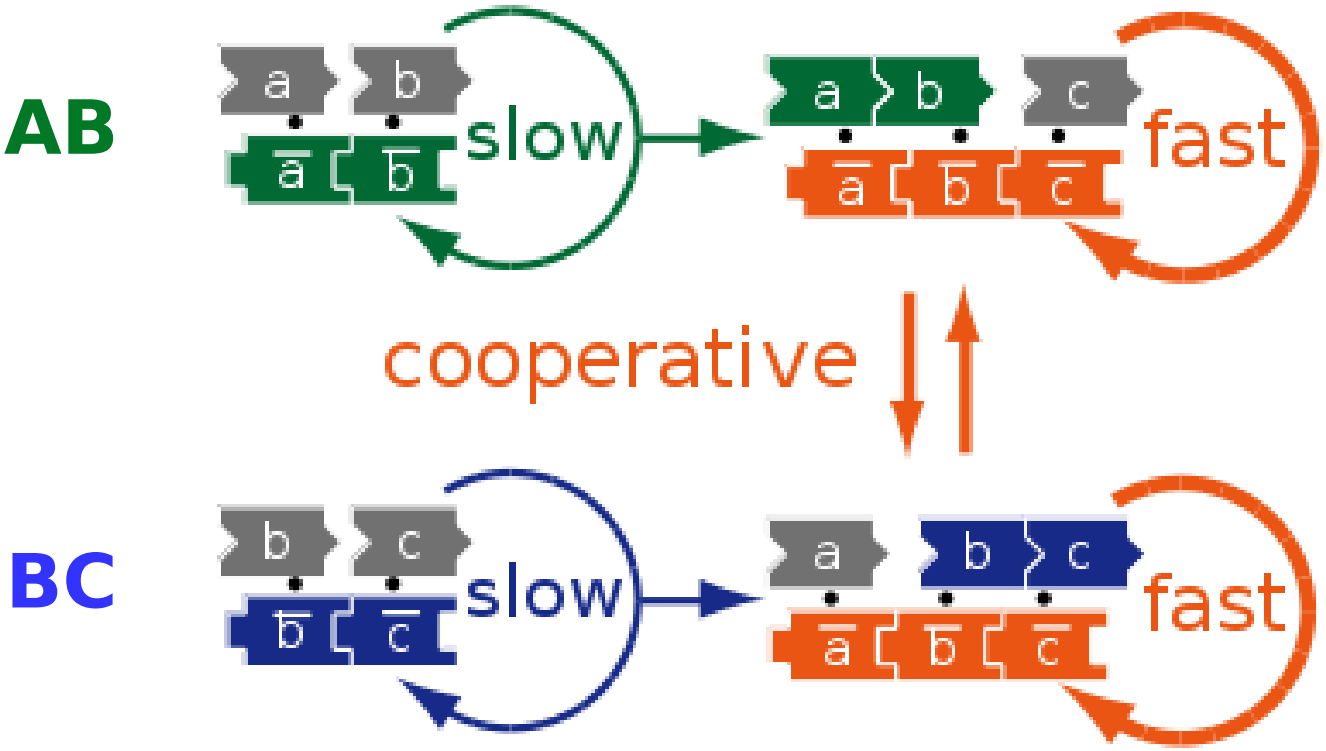


Exp. Replication by feeding b,c,$\bar{b}$,$\bar{c}$

Cooperative Replication by Competitive Ligation?

Exp. Replication by feeding a,b,$\bar{a}$,$\bar{b}$

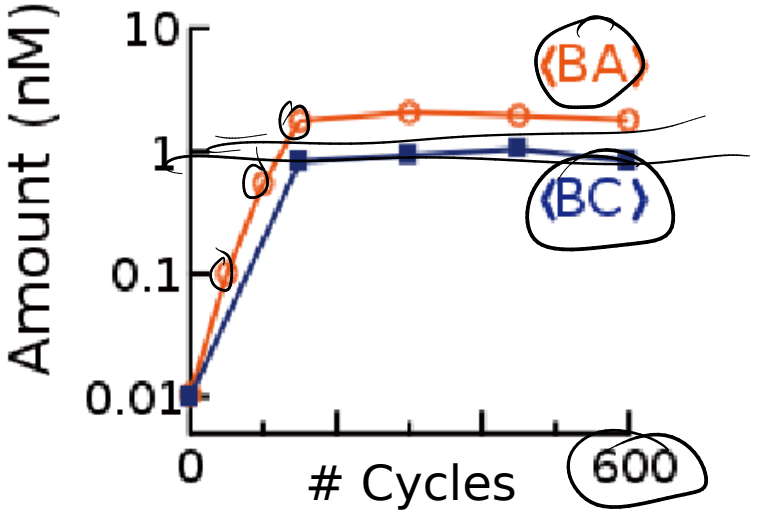
Cooperative Sequence



Exp. Replication by feeding b,c,$\bar{b}$,$\bar{c}$

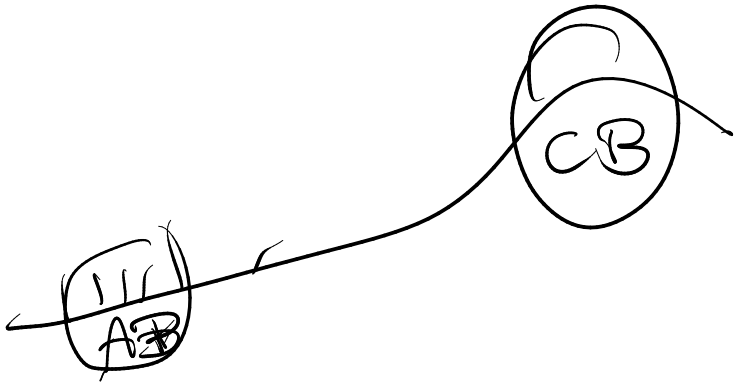
Hypothesis: Hyper-exponential growth of Cooperative Sequences

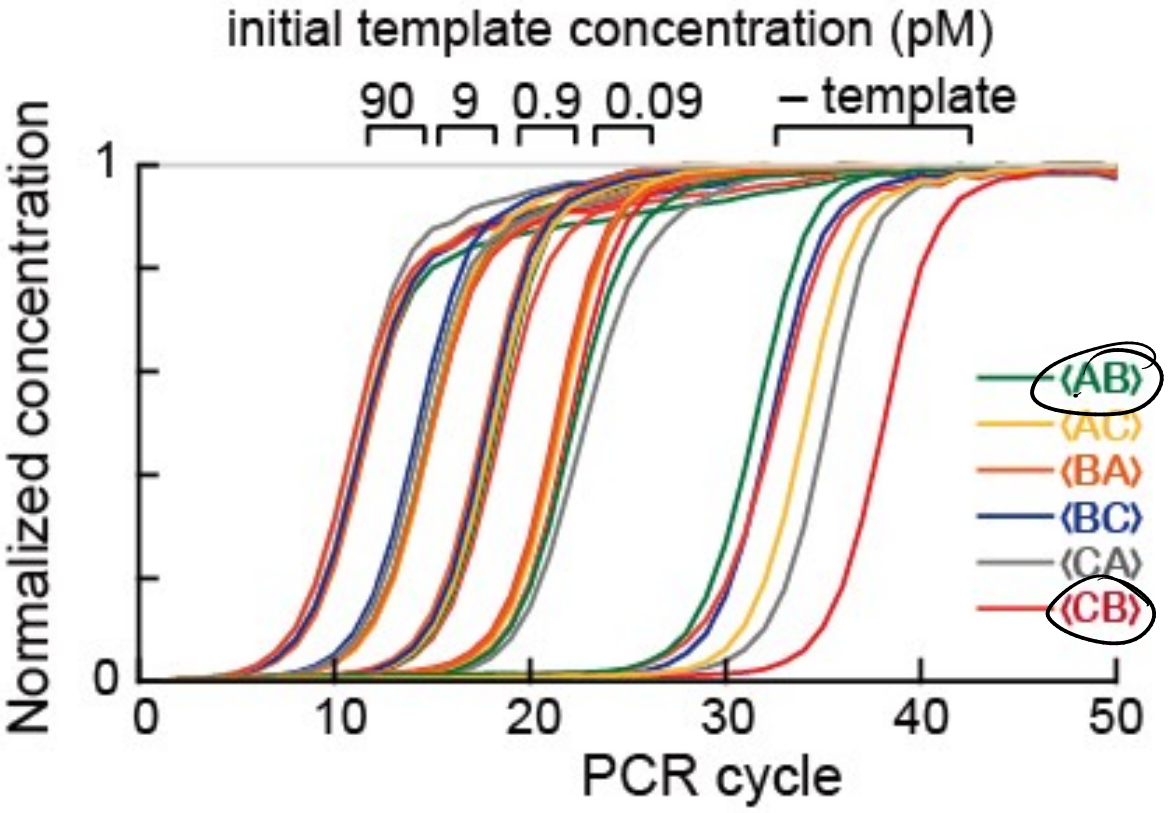
Cooperative Replication by Ligation?



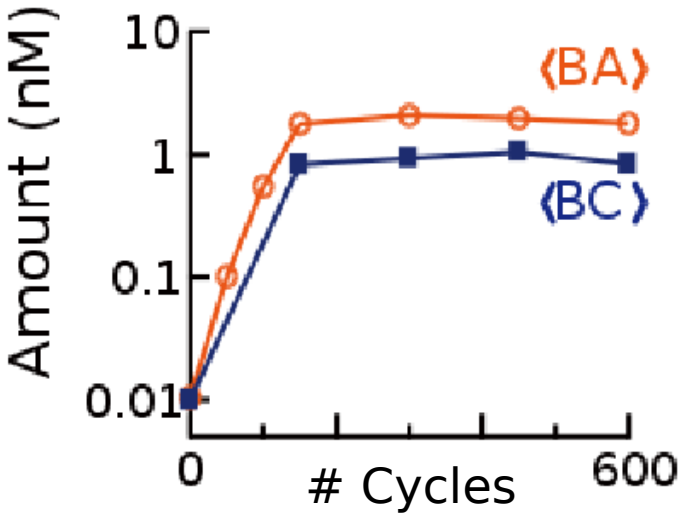
- Feeding with 20-mers B,C,A
- Degradation by serial dilution
- Temperature cycling for reshuffling

BA and BC replicate to steady state

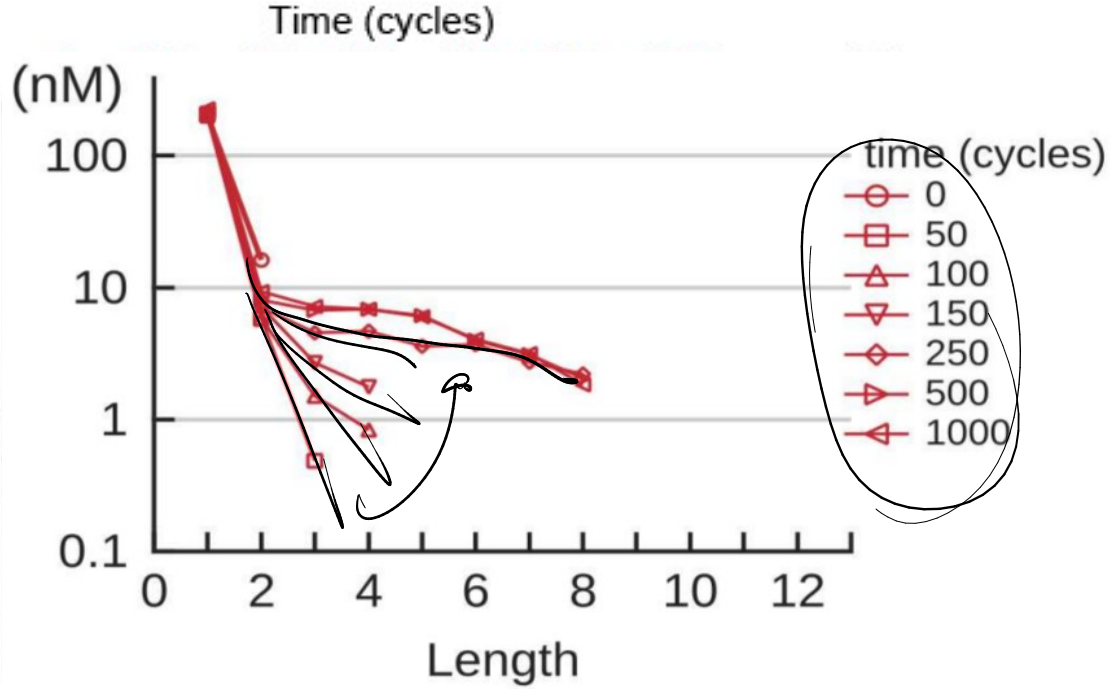


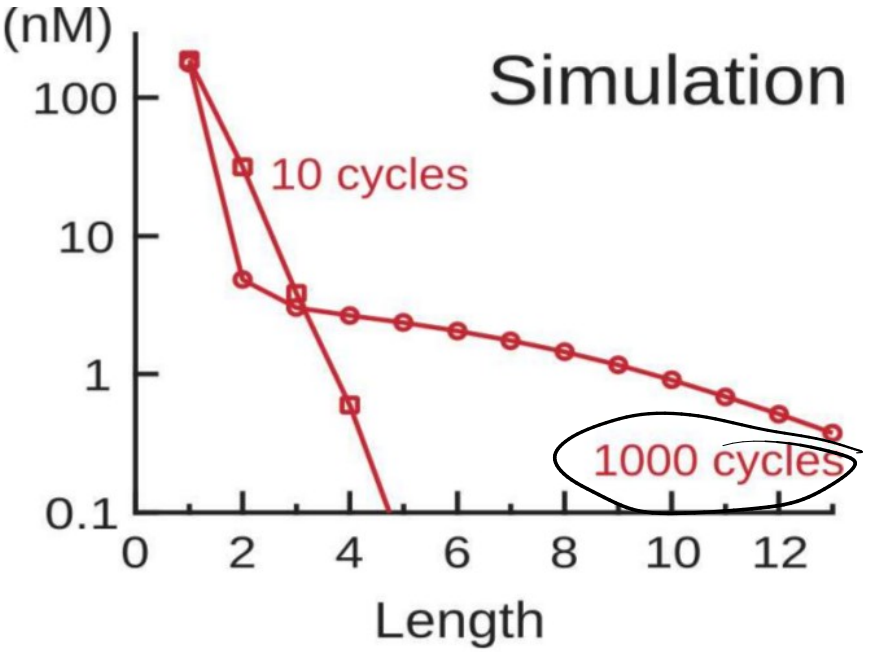


Cooperative Replication by Ligation?

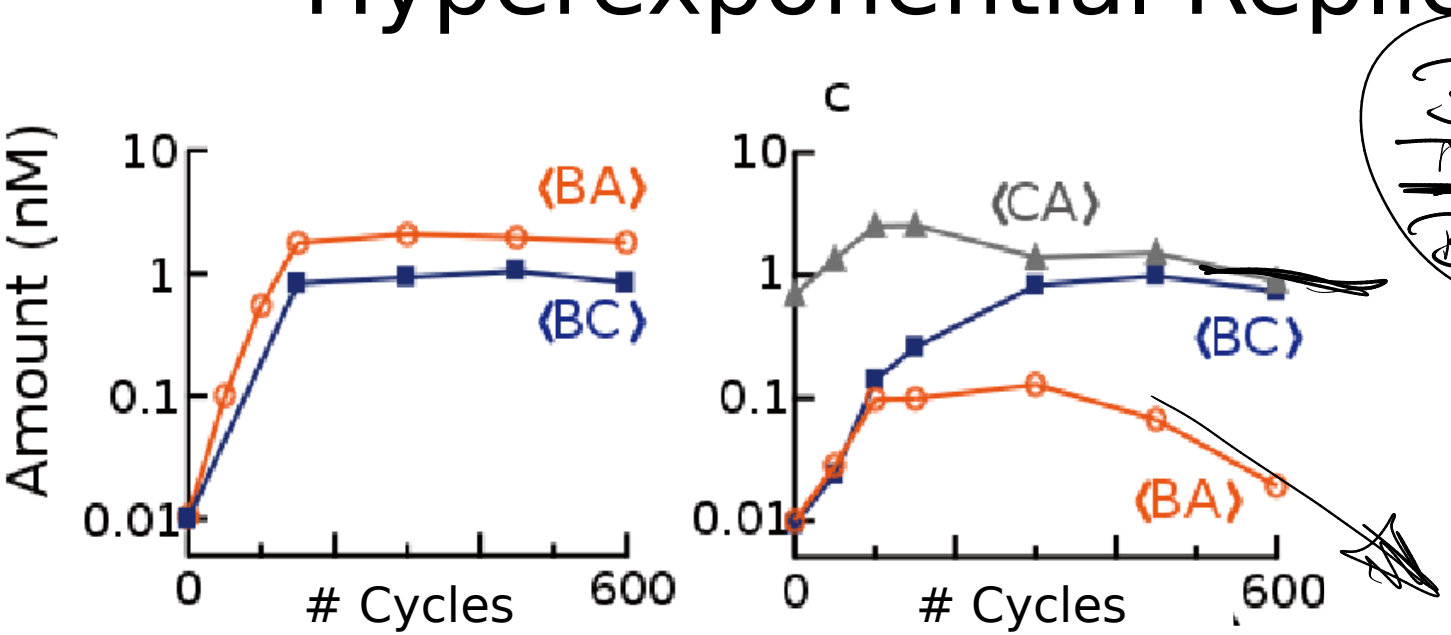


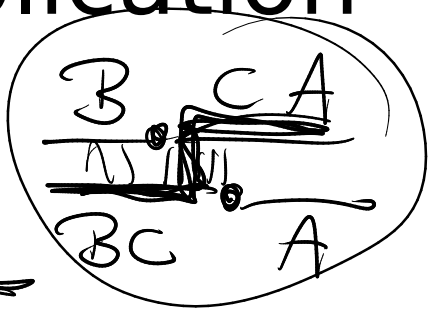
BA and BC replicate to steady state





Hyperexponential Replication



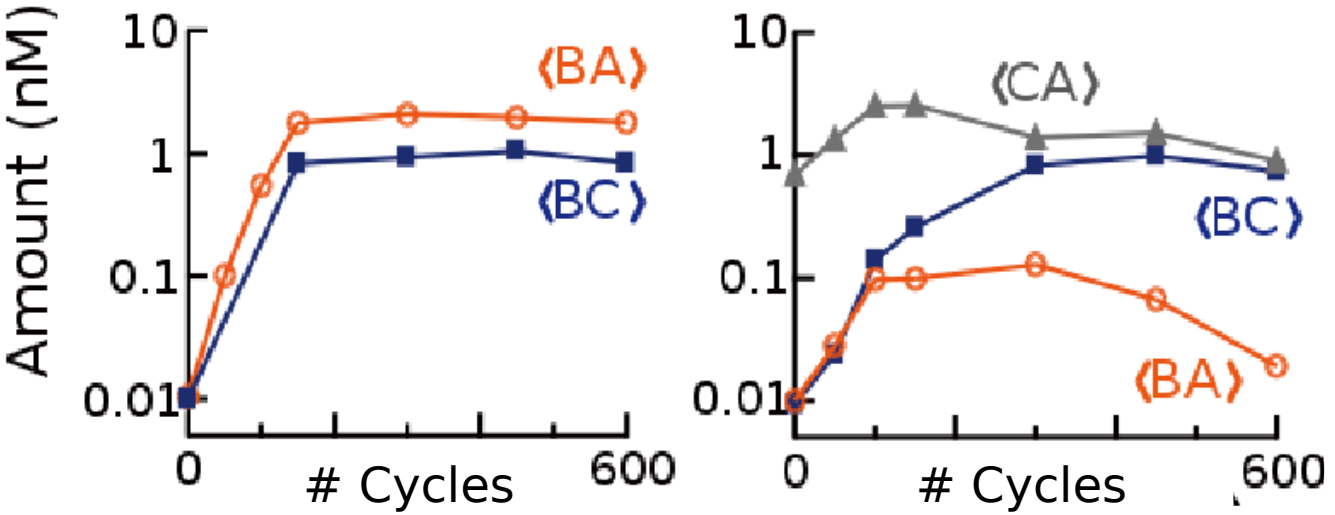


Seeding with CA makes BA die out

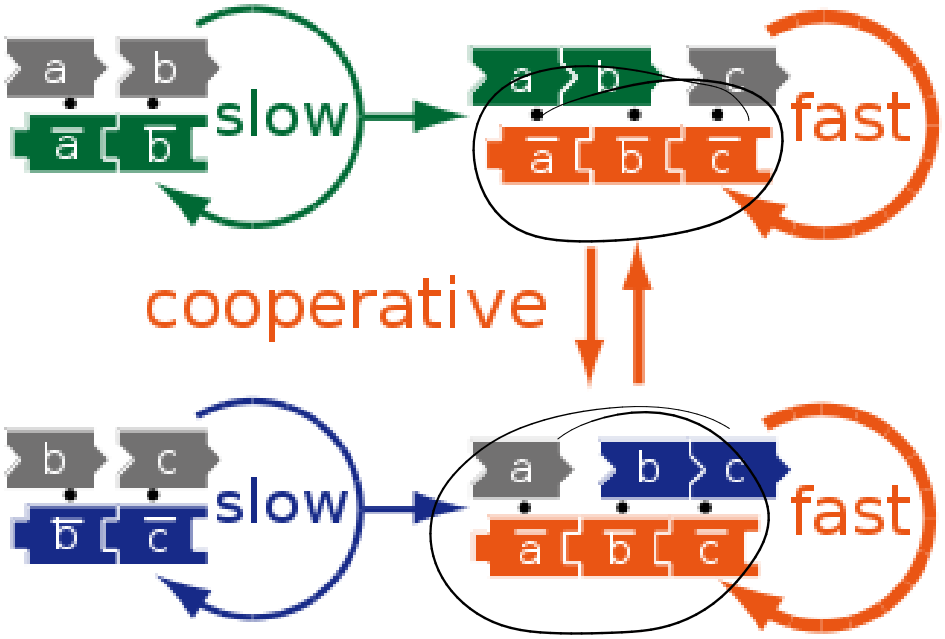
BA

BC

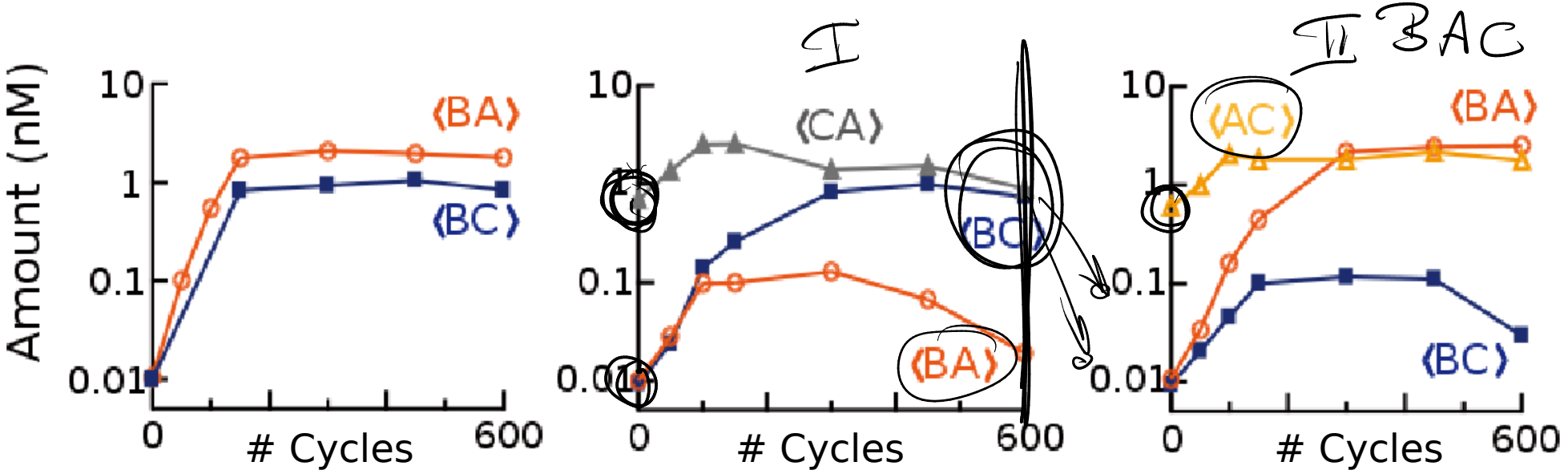
Hyperexponential Replication



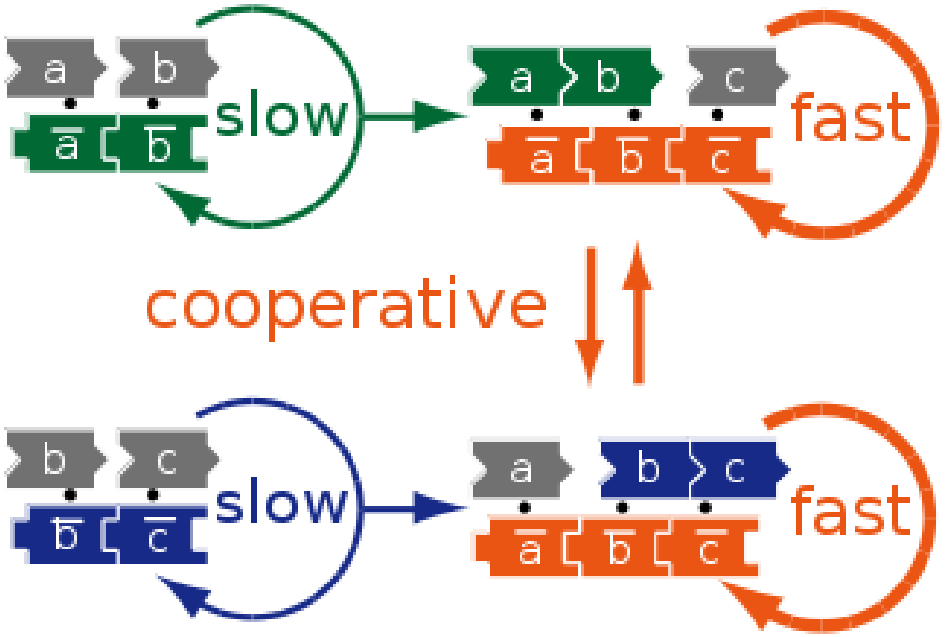
...BCA...



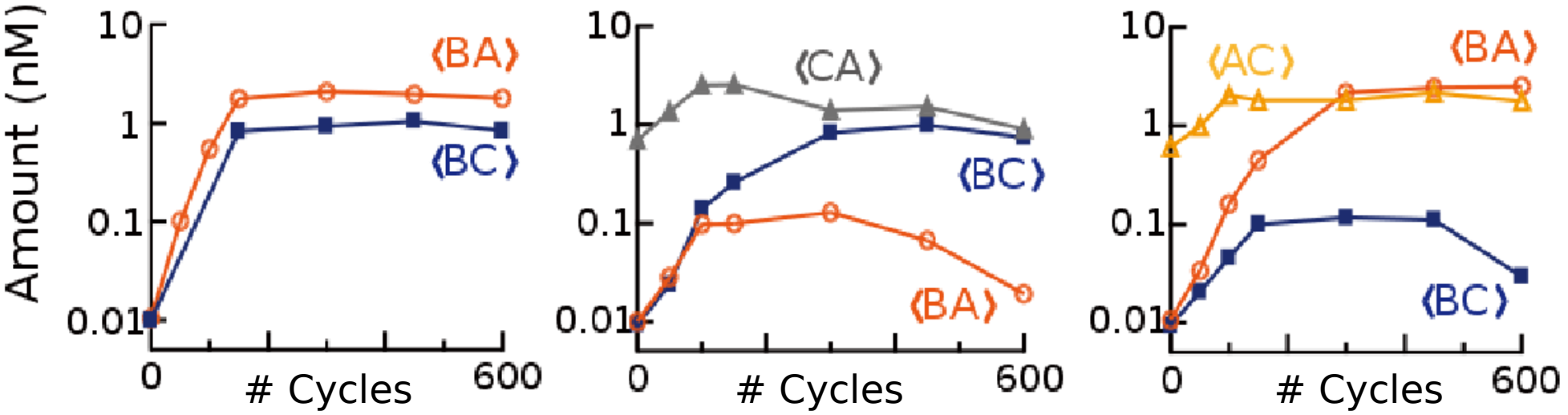
Hyperexponential Replication



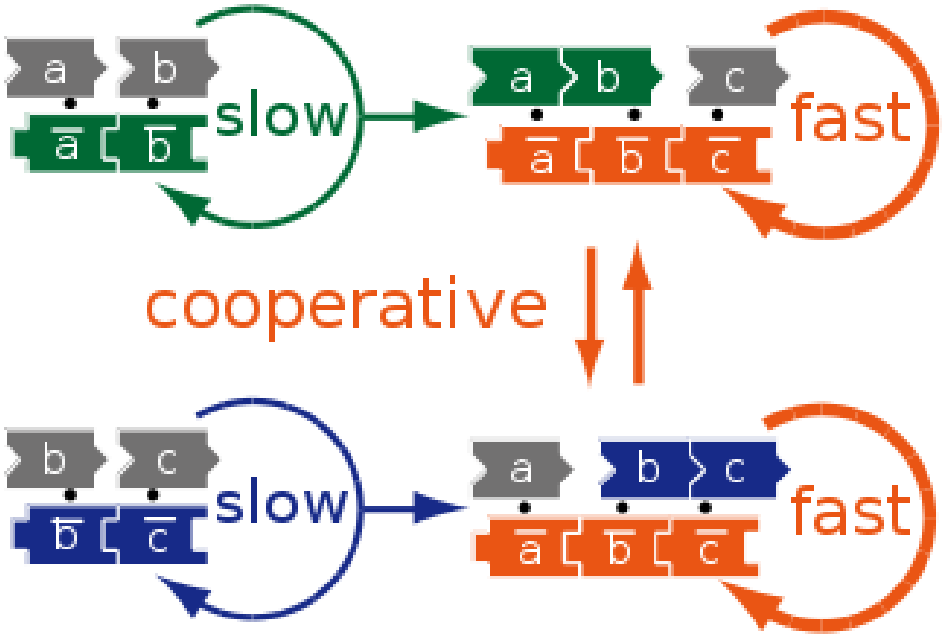
...BCA... **...BAC...**



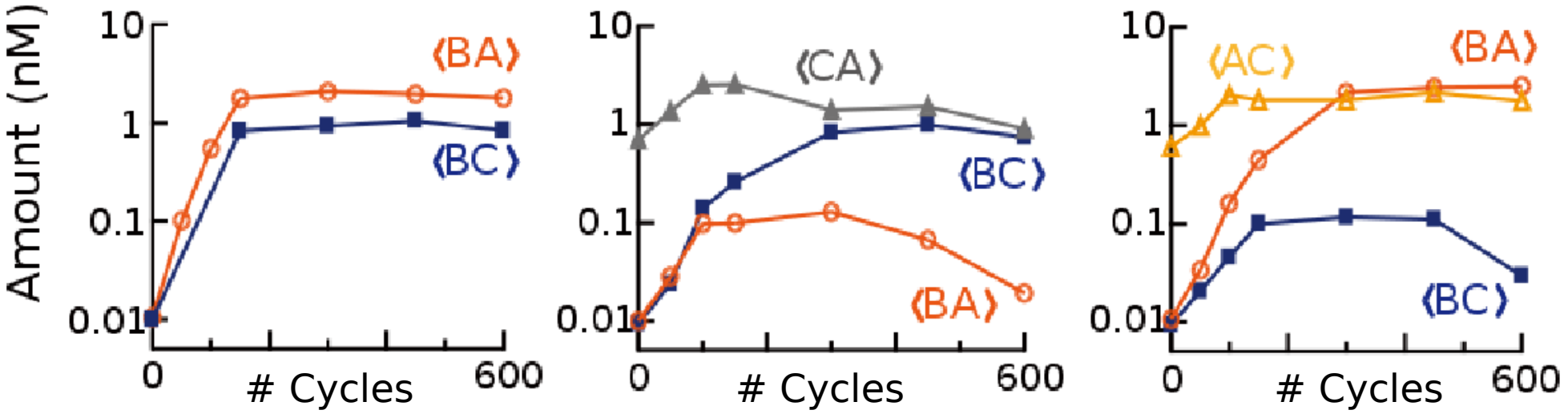
Hyperexponential Replication



...BCA... **...BAC...**

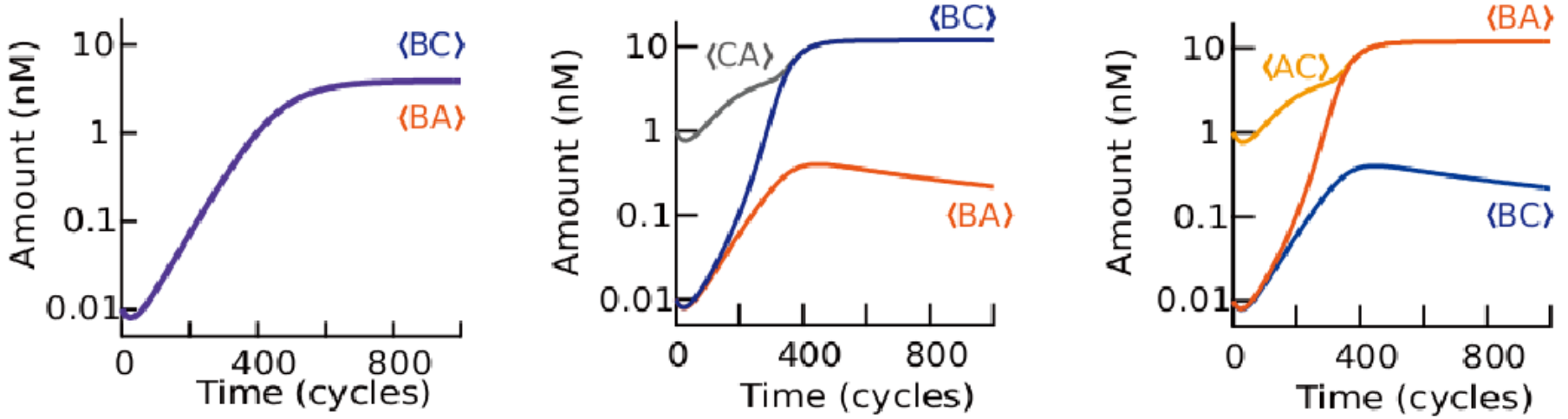


Hyperexponential Replication

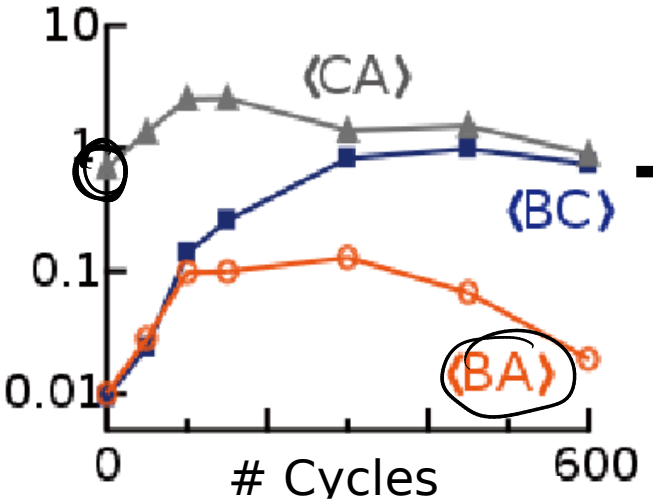


...BCA... **...BAC...**

Theory

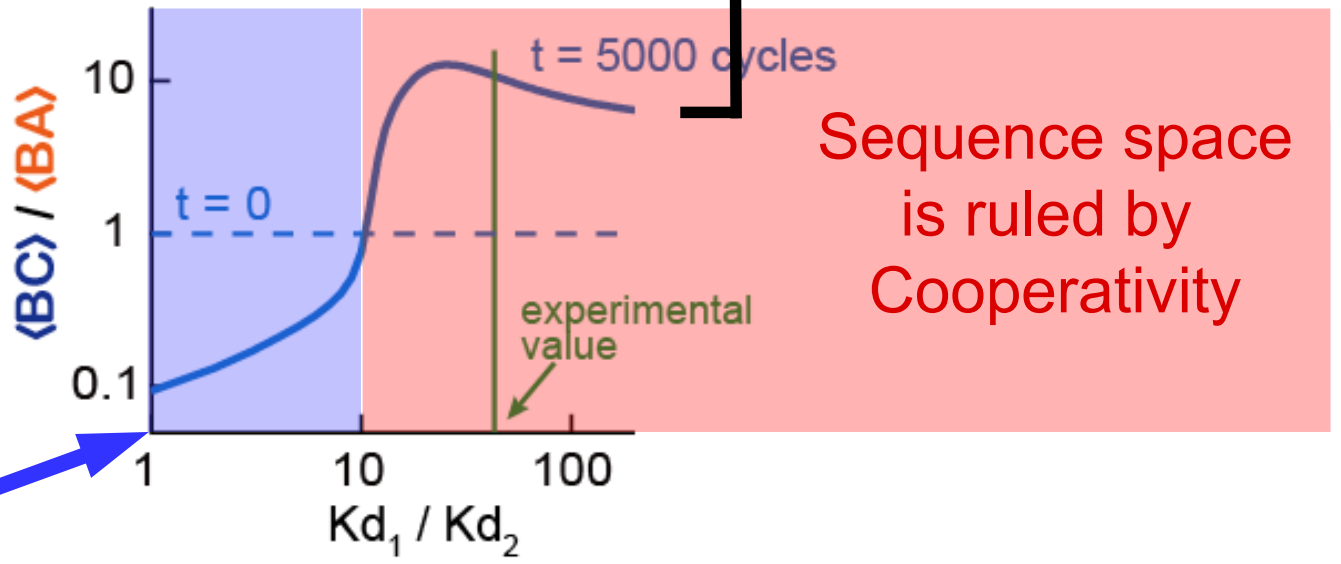


Hyperexponential Replication



Cooperation Level

Simulation with 30% thermodynamic bias for ligation of BA

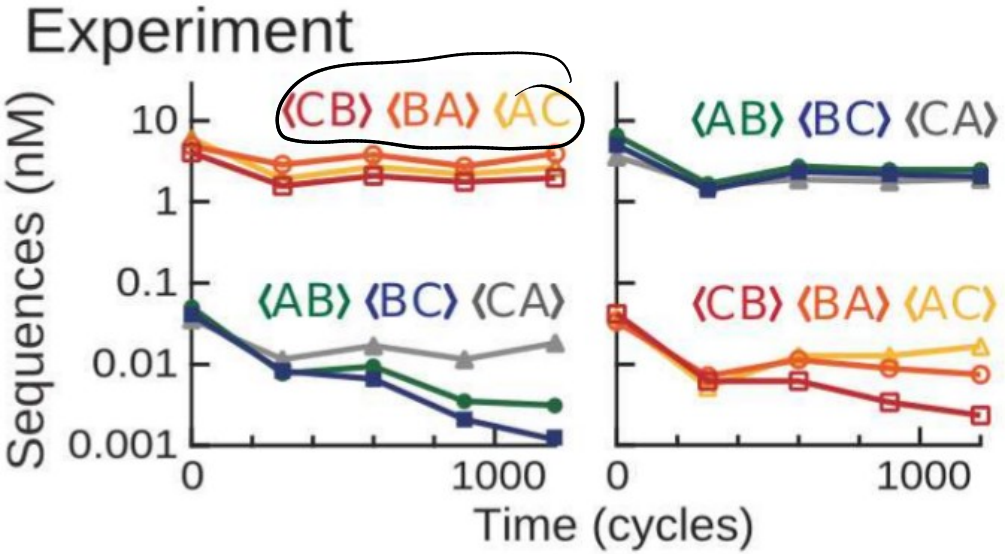


Sequence space is ruled by Cooperativity

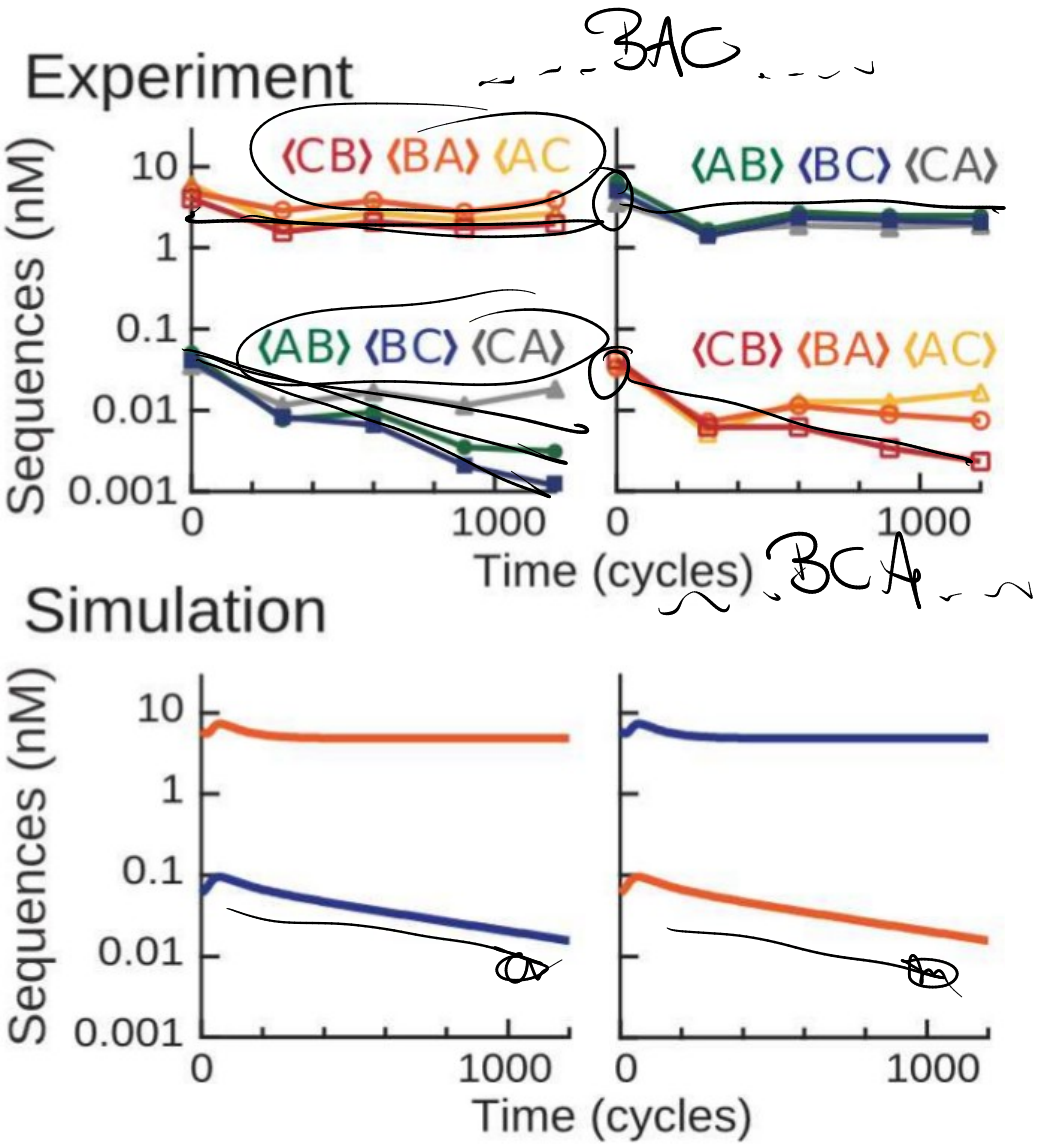
Sequence space is ruled by Thermodynamics

Competition of Ligation

Past Majority dominates present Minority
(frequency dependent replication)



Generation of Sequence Species against Diffusion



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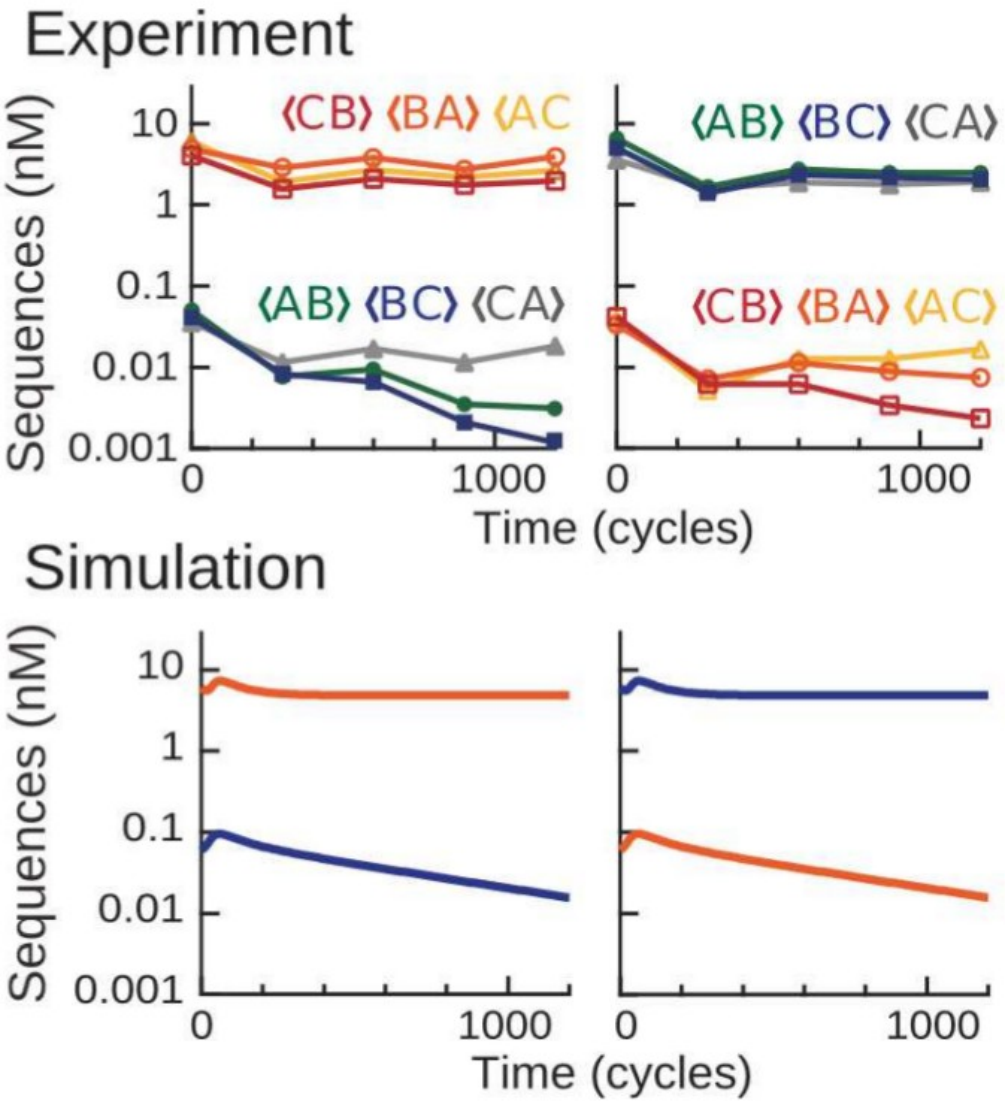

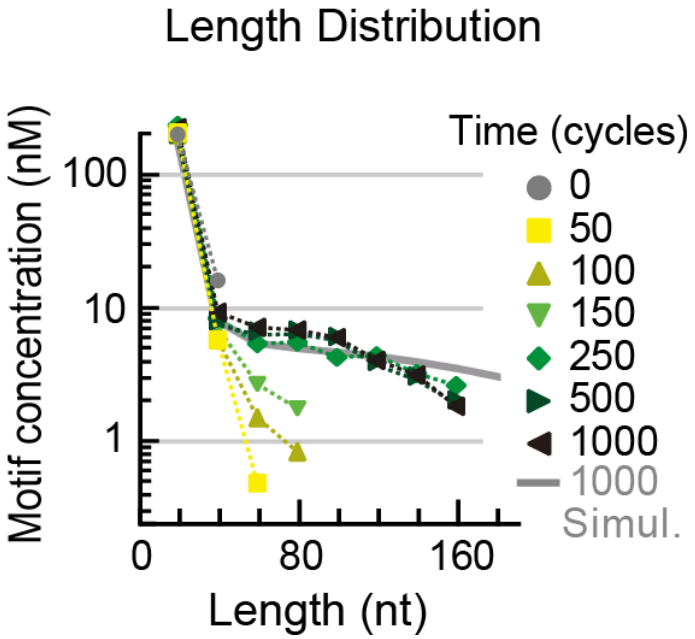

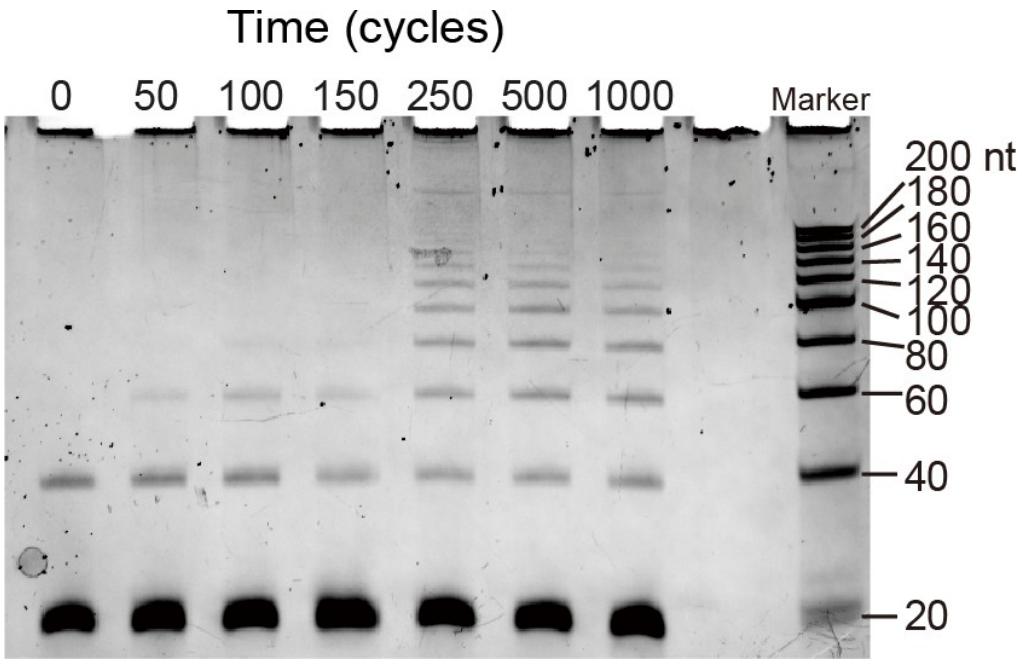

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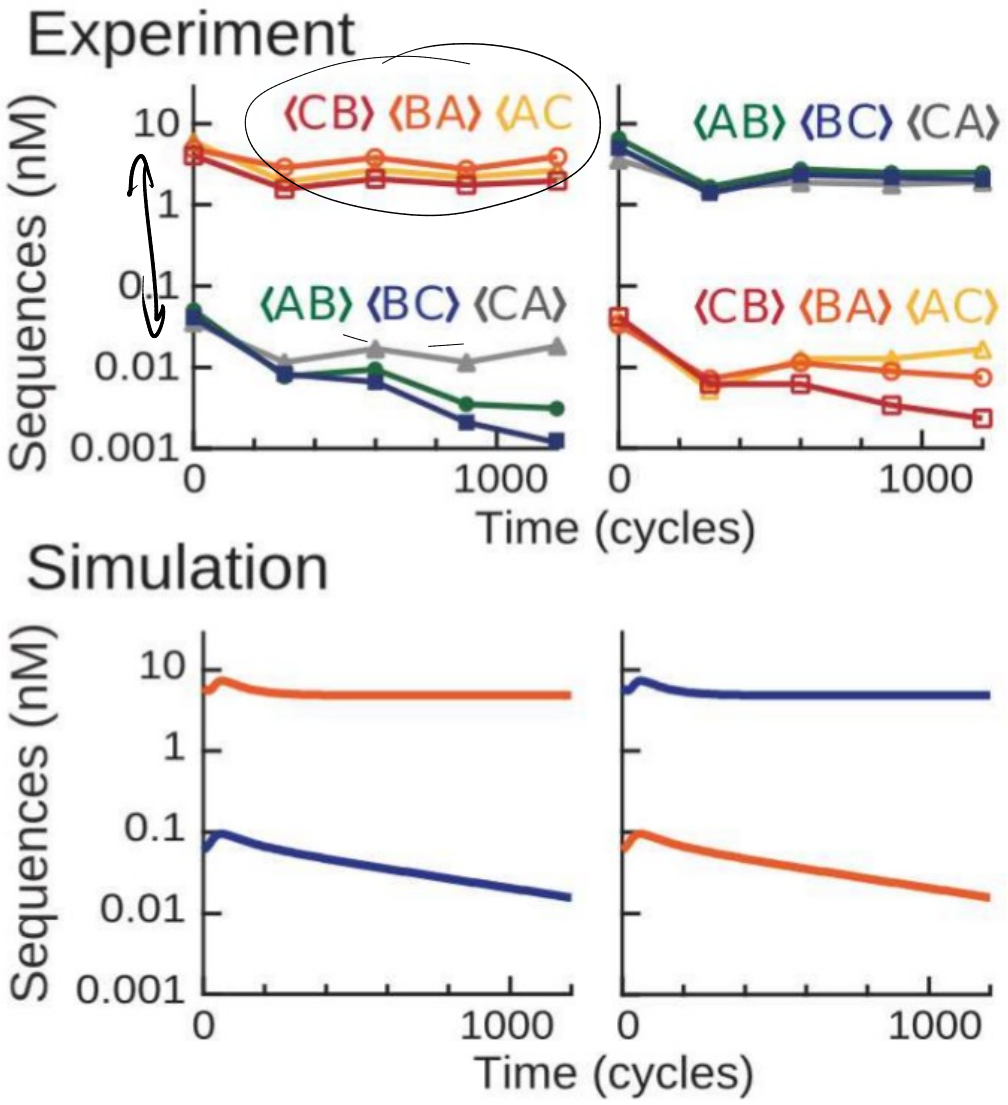

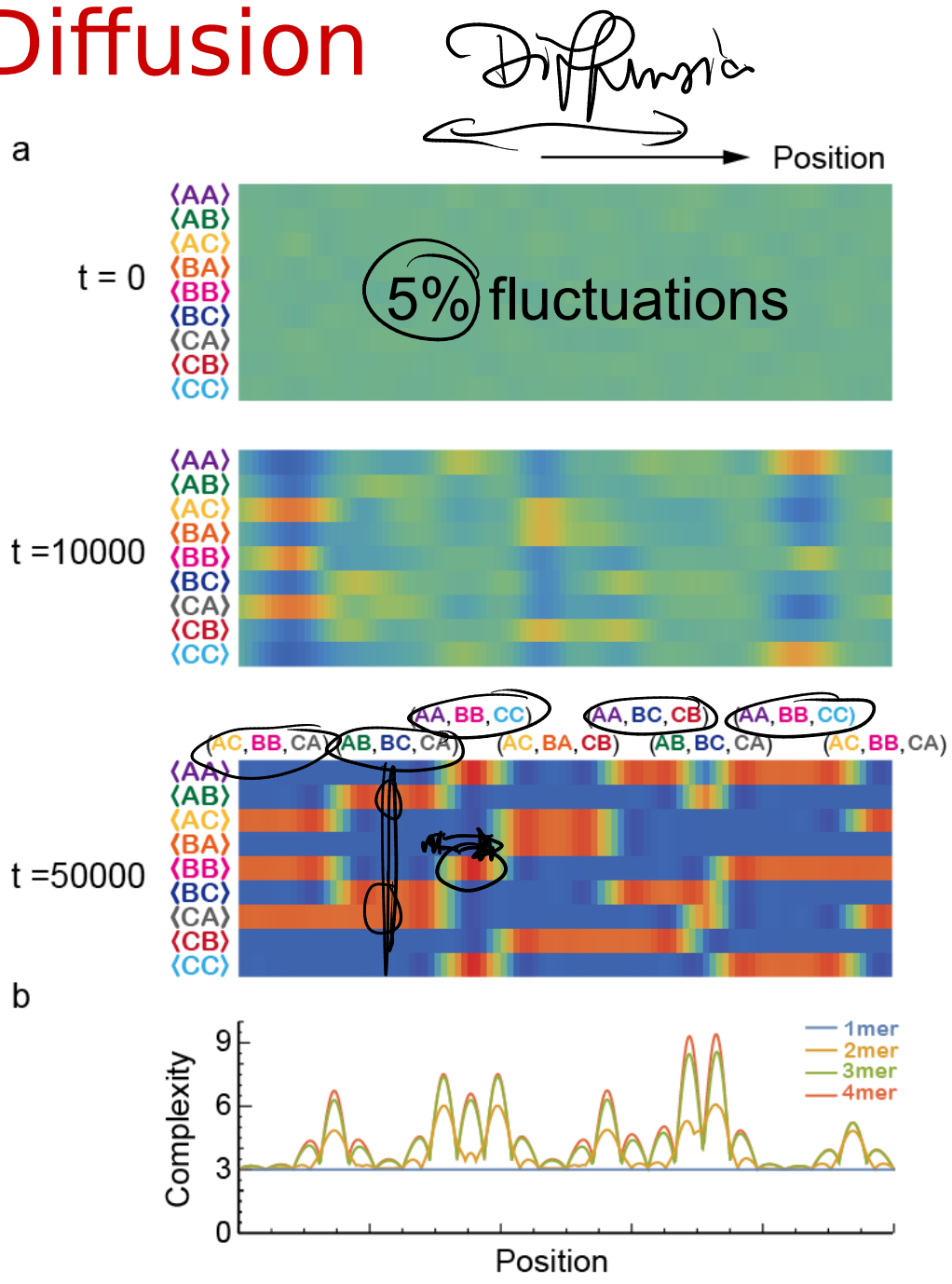

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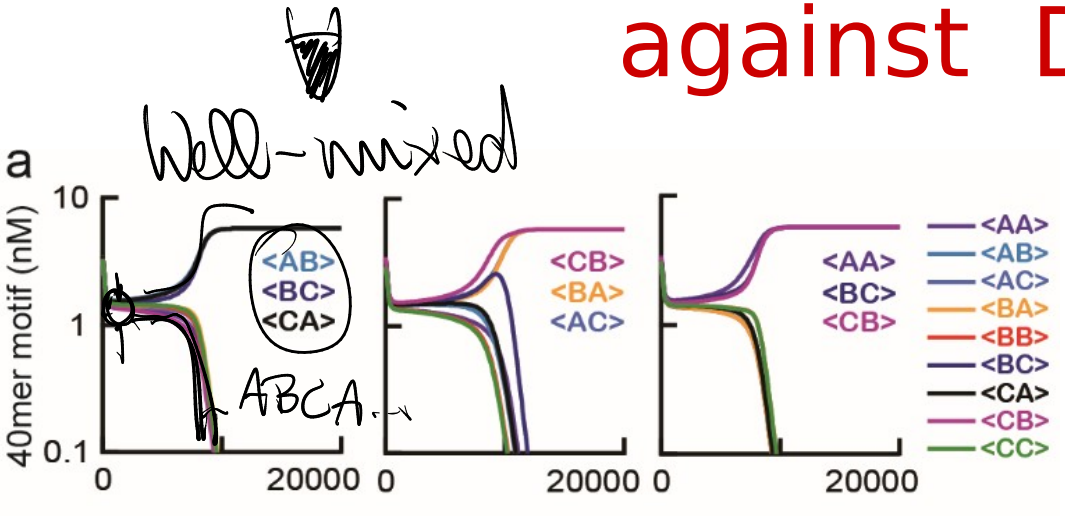

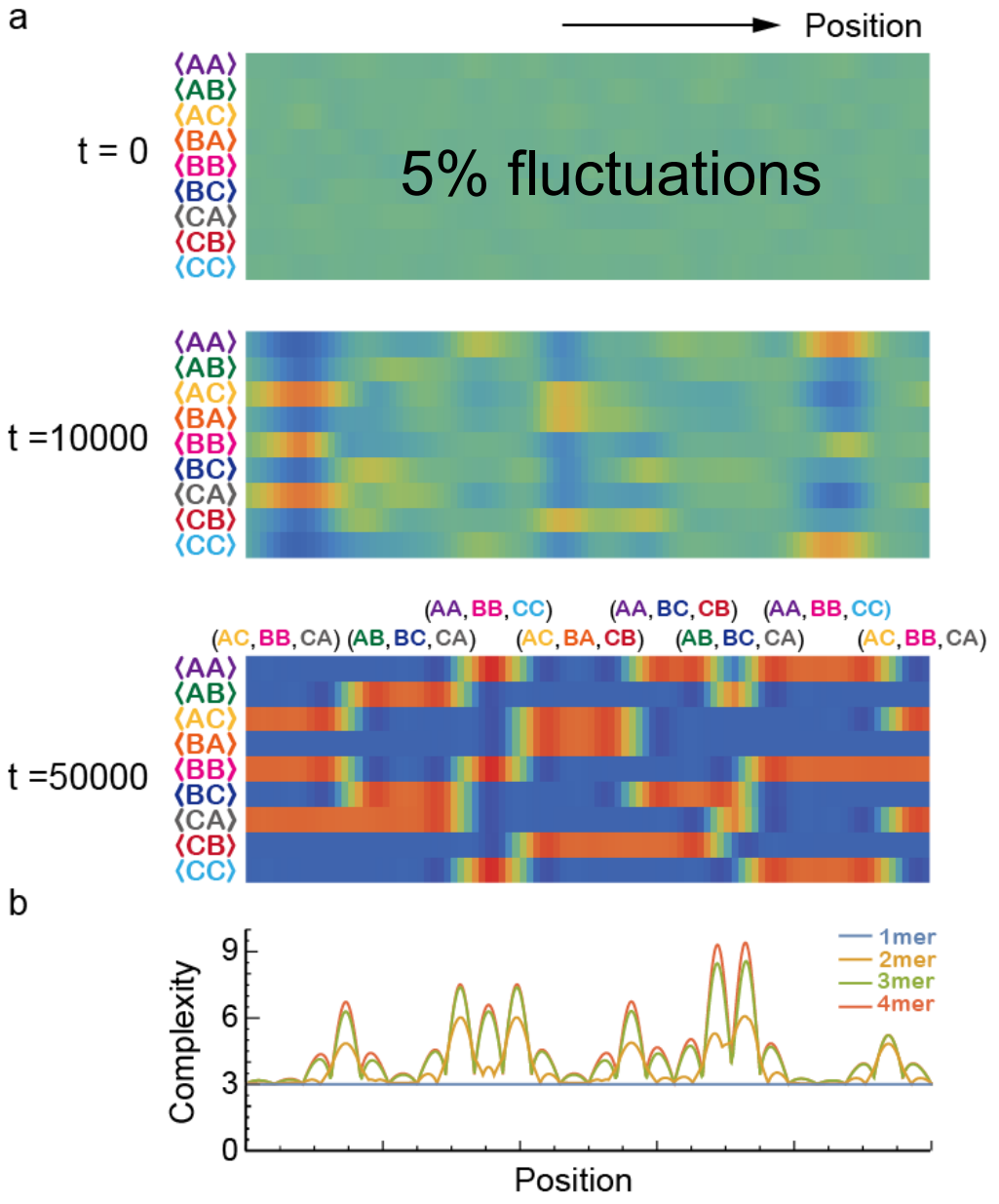

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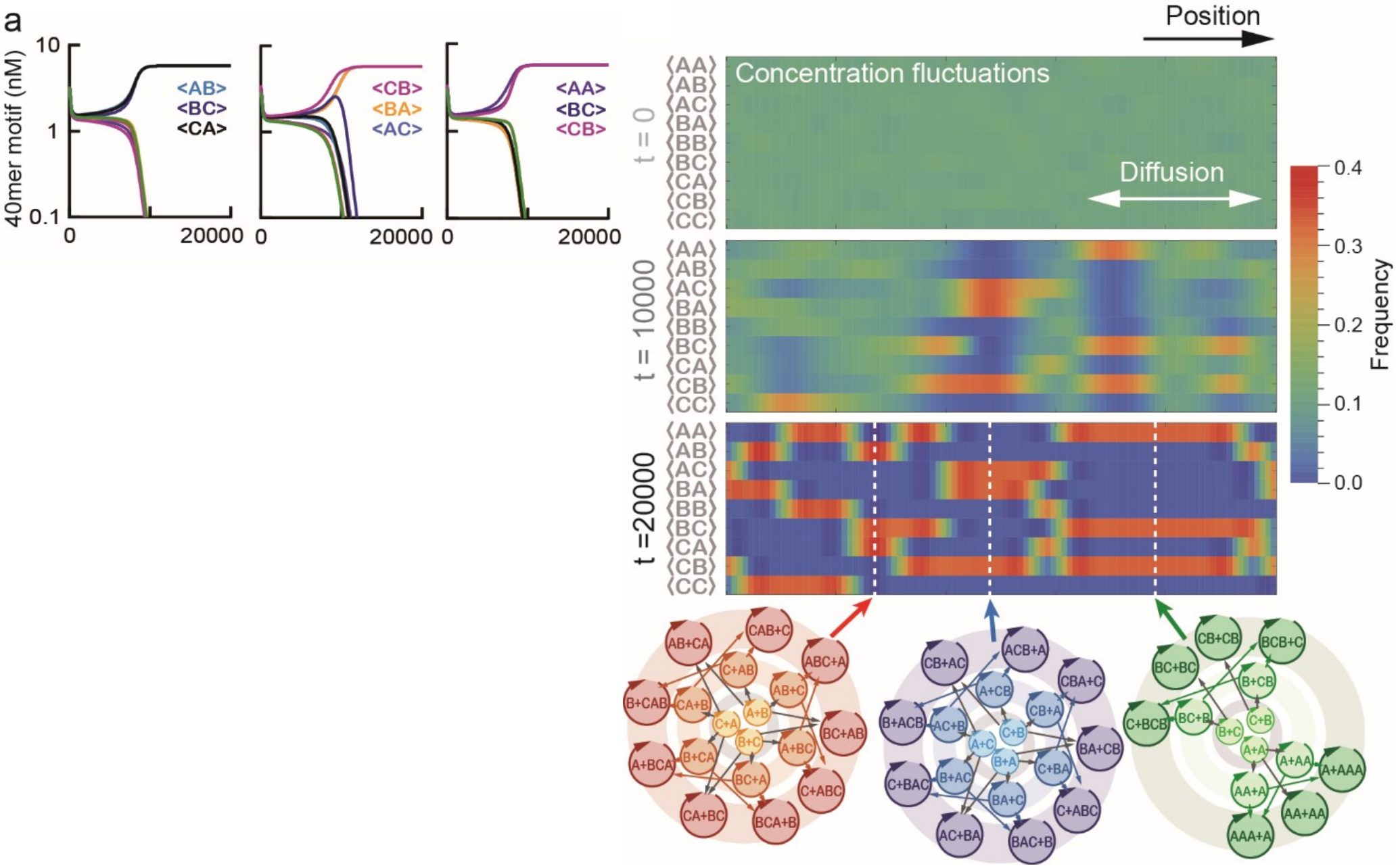

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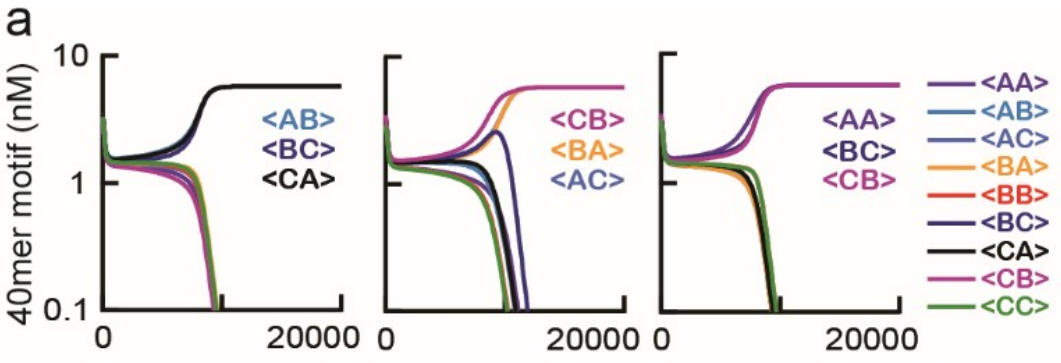

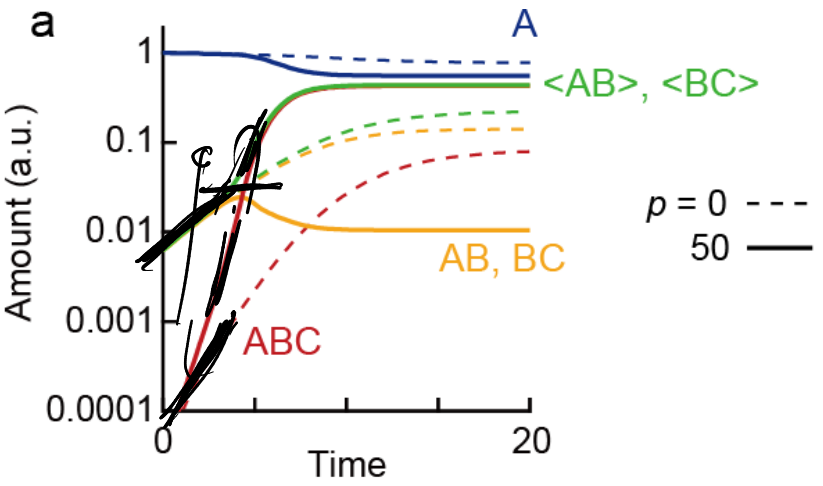

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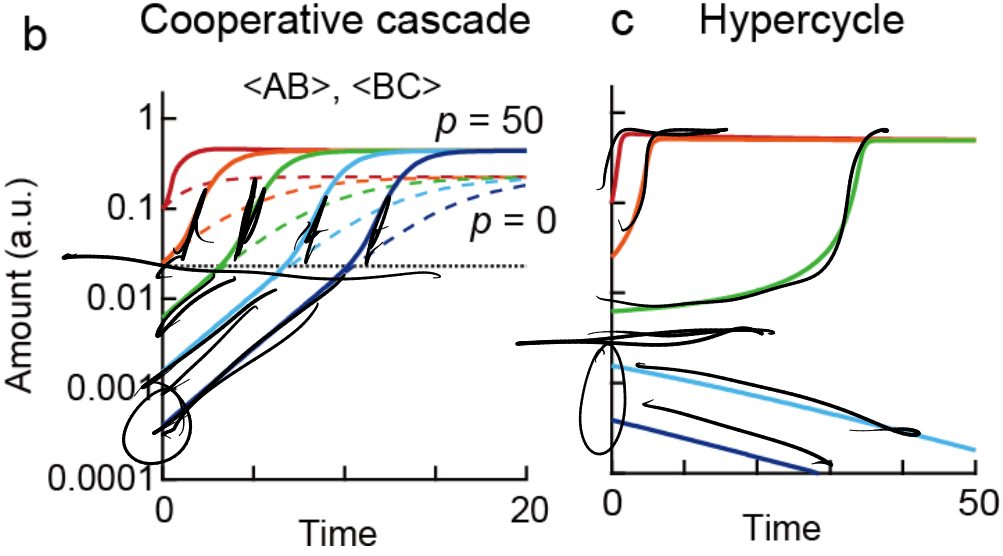

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Generation of Sequence Species against Diffusion

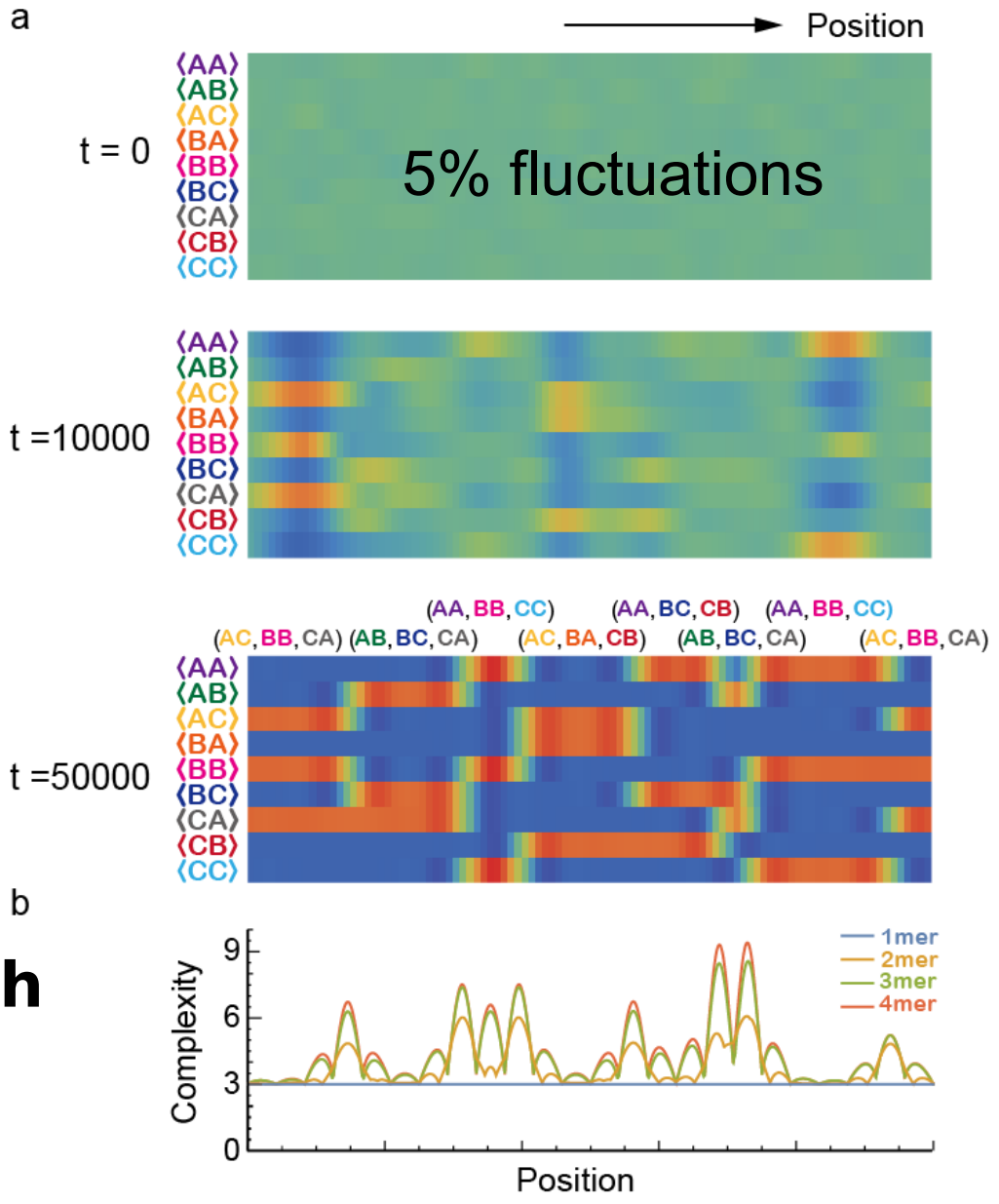
Summary

Competition of ligation creates cooperativity of sequences

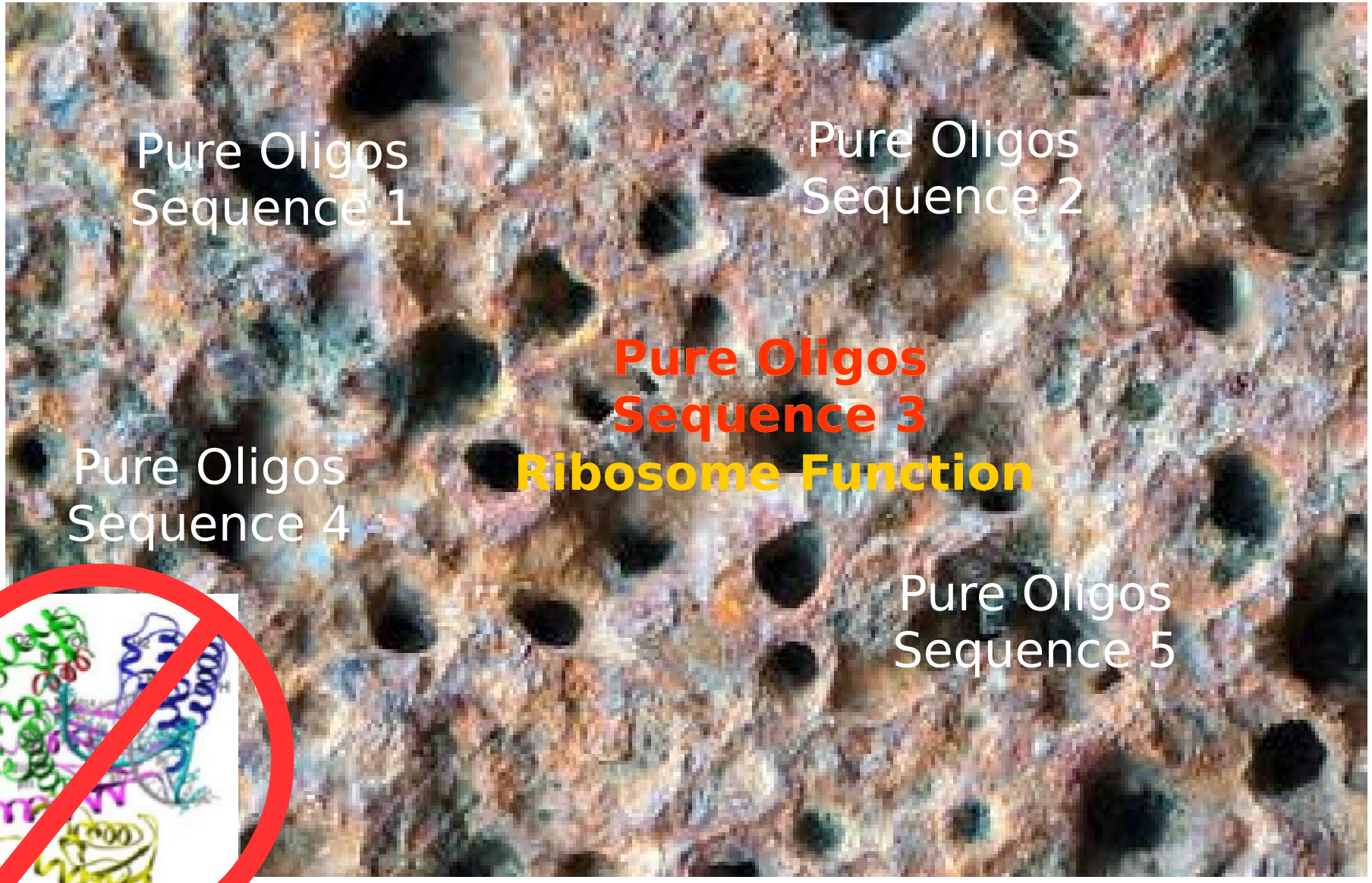
Hyperexponential support of cooperative sequence patterns in replication by ligation

Overcomes the tyranny of thermodynamics and allows complex sequences

Emergence of species in both real and sequence space.



Generation of Sequence Species against Diffusion



Taq Ligase (much simpler chemistry)